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Oral xanthines as maintenance treatment for asthma in children (Review)

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[Intervention Review]

Oral xanthines as maintenance treatment for asthma in children

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ABSTRACT

Background

Xanthines have been used in the treatment of asthma as a bronchodilator, though they may also have anti-inflammatory effects. The current role of xanthines in the long-term treatment of childhood asthma needs to be reassessed.

Objectives

To determine the efficacy of xanthines (e.g. theophylline) in the maintenance treatment of paediatric asthma.

Search methods

A search of the Cochrane Airways Group Specialised Register was undertaken with predefined search terms. Searches are current to May 2008.

Selection criteria

Randomised controlled trials, lasting at least four weeks comparing a xanthine with placebo, regular short-acting beta-agonist (SABA), inhaled corticosteroids (ICS), cromoglycate (SCG), ketotifen (KET) or leukotriene antagonist, in children with diagnosed with chronic asthma between 18 months and 18 years old.

Data collection and analysis

Two reviewers independently selected each study for inclusion in the review and extracted data. Primary outcome was percentage of symptom-free days.

Main results

Thirty-six studies (2838 participants) were included. **Xanthine versus placebo (18 studies):** The proportion of symptom free days was larger with xanthine compared with placebo (7.97% [95% CI 3.41, 12.53]). Rescue medication usage was lower with xanthine, with no significant difference in symptom scores or hospitalisations. FEV_1, and PEF were better with xanthine. Xanthine was associated with non-specific side-effects. Data from behavioural scores were inconclusive. **Xanthine versus ICS (four studies) :** Exacerbations were less frequent with ICS, but no significant difference on lung function was observed. Individual studies reported significant improvements in symptom measures in favour of steroids, and one study reported a difference in growth rate in favour of xanthine. No difference was observed for study withdrawal or tremor. Xanthine was associated with more frequent headache and nausea. **Xanthine versus regular SABA (10 studies):** No significant difference in symptoms, rescue medication usage and spirometry. Individual studies reported improvement in PEF with beta-agonist. Beta-agonist treatment led to fewer hospitalisations and headaches. Xanthine was associated with

less tremor. **Xanthine versus SCG (six studies):** No significant difference in symptoms, exacerbations and rescue medication. Sodium cromoglycate was associated with fewer gastro-intestinal side-effects than xanthine. **Xanthine versus KET (one study):** No statistical tests of significance between xanthine and ketotifen were reported. **: Xanthine + ICS versus placebo + same dose ICS (three studies) :** Results were conflicting due to clinical/methodological differences, and could not be aggregated. **Xanthine + ICS versus ICS + leukotriene (one study):** Results from one trial One small parallel study did not measure the primary outcome of symptoms; differences between treatments in end of treatment values were not statistically significant.

Authors' conclusions

Xanthines as first-line preventer alleviate symptoms and reduce requirement for rescue medication in children with mild to moderate asthma. When compared with ICS they were less effective in preventing exacerbations. Xanthines had similar efficacy as single preventative agent compared with regular SABA and SCG. Evidence on AEs (adverse effects) was equivocal: there was evidence for increased AEs overall, but no evidence that any specific AE (including effects on behaviour and attention) occurred more frequently than with placebo. There is insufficient evidence from available studies to make firm conclusions about the effectiveness of xanthines as add-on preventative treatment to ICS, and there are no published paediatric studies comparing xanthines with alternatives in this role. Our data suggest that xanthines are only suitable as first-line preventative asthma therapy in children when ICS are not available. Pre-trial exposure to the agents assessed may have pre-disposed the trial populations to tolerate the drug, and may have threatened blinding. They may have a role as add-on therapy in more severe asthma not controlled by ICS, but further studies are needed to examine this, and to define the risk-benefit ratio compared with other agents.

PLAIN LANGUAGE SUMMARY

The effects of oral xanthines (e.g. theophylline) for chronic asthma in children

Xanthines (e.g. theophylline) are a group of drugs thought to have helpful preventative and reliever properties in the treatment of asthma in children. This review of studies has established that there is evidence for useful effects of these drugs in terms of symptom relief and lung function, but also some evidence of side-effects. As a *primary preventative therapy*, whilst there is evidence that xanthines are effective, this review suggests that more effective alternative treatment options (inhaled steroids) are available. In children with more severe asthma, the role of xanthines as an *add-on therapy* has only been assessed in a small number of trials, which report mixed effects. More studies in this area would help to generate a more reliable overview of the effects of treatment in these children. Xanthines are an effective preventative treatment in childhood asthma, but less effective than inhaled steroids, and with a less favourable side-effect profile. There is insufficient evidence at present to assess their role as "add-on" preventer treatment versus newer alternatives. Some of the trials exposed the children they recruited to a pre-trial phase of xanthine in order to maintain effective dosing during the trial. This could have made the trial participants less representative of the general population by making them more inclined to tolerate the study drug. This exposure also may have meant that they could recognise what drug they were taking during the blinded phase of the study.

BACKGROUND

Xanthines, such as theophylline and aminophylline, have been used as bronchodilators for many years in the treatment of asthma (Hermann 1937). A number of controlled clinical trials have confirmed the efficacy of xanthines as bronchodilators (Weinberger 1974), but side-effects have been a concern (Stein 1993). With the recognition of inflammation in the pathogenesis of asthma, use of theophyllines has declined in many countries (Vassallo 1998). Aggressive treatment of airway inflammation with agents such as inhaled steroids is now recommended by consensus statements on asthma (IPACG 1992, NHLBI 2002; BTS 2003). Such statements recommend theophyllines only as 'add-on' treatment when control is not achieved by inhaled steroids, and increasingly as second or third choice in this role (BTS 2003).

More recently, interest in xanthines has been reawakened by evidence suggesting a mild anti-inflammatory, as well as bronchodilator, effect of these drugs (Pauwels 1989), though whether this is clinically relevant remains controversial. Although adult studies have provided good evidence for long-acting beta-agonists as first choice 'add-on' treatment to inhaled steroids (Greening 1994; Ind 2003), evidence for this in children is lacking (Verberne 1998), and there have been no direct comparisons with xanthines or leukotriene antagonists in paediatrics. Worldwide, particularly in developing countries where cost and availability are major issues, xanthines are potentially even more important (Kabra 2003). A review of the literature summarizing the evidence regarding the use of xanthines in the maintenance treatment of childhood asthma is warranted.

OBJECTIVES

To review the efficacy of oral xanthines as maintenance treatment of chronic childhood asthma. Use of intravenous aminophylline in acute asthma was not included.

The specific questions to be answered were:
1. Is xanthine as maintenance therapy effective in improving asthma control as compared to placebo, beta-agonist, inhaled corticosteroid, ketotifen, cromoglycate or leukotriene antagonists?
2. Does the use of xanthine result in an excess of adverse effects compared with placebo or the alternative maintenance therapies?

Two separate treatment comparisons were made:
1. Use of xanthine as a single agent
2. Use of xanthine as 'add-on' treatment to inhaled corticosteroids (i.e. with inhaled corticosteroids as a co-intervention)

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) were eligible for inclusion in the review.

Types of participants

Children (under 18 years) with physician-diagnosed chronic asthma. Studies which only recruited children under 18 months were excluded because of the diagnostic difficulties in infants. Studies which included children under 18 months were considered in the review. Participants should have received an oral xanthine for the treatment of symptoms, for a minimum period of one month.

We excluded studies on exercise induced bronchoconstriction (EIB), and studies in acute asthma.

Types of interventions

We considered the effects of xanthines in three comparative settings. Participants must have been randomised to receive, for a minimum of four weeks, either an oral xanthine (theophylline, choline theophyllinate or aminophylline) given at any dose (active intervention) or one of the following control interventions: placebo, regular beta-agonist, inhaled corticosteroid, ketotifen, cromoglycate or a leukotriene antagonist.

For treatment comparison one, no additional co-intervention was permitted other than rescue short-acting beta-2 agonists or systemic steroids.

For treatment comparison two, all patients had to receive inhaled corticosteroids as standard co-intervention.

Types of outcome measures

Primary outcomes

Proportion of days with no symptoms.

Secondary outcomes

1. Symptom score
2. Proportion of days with no use of rescue short-acting beta-2 agonists
3. Rate of exacerbations requiring rescue oral steroids/hospital admissions
4. Lung function (change from baseline)
5. Average beta-2 agonist use
6. Measures of bronchial hyperreactivity (including graded bronchoconstrictor challenge, exercise challenge, and measures of peak flow variability)
7. Adverse effects (including death, vomiting, headache, seizures, impaired learning and other psychomotor effects)
8. Withdrawal rate

Search methods for identification of studies

Electronic searches

Trials were identified using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts (please see the Airways Group Module for further details). All records in the Specialised Register coded as 'asthma' were searched using the following terms:

(theophylline* or aminophyllin* or methyl-xanthin* or methylxanthin* or xanthin*) and (child* or paediat* or pediat* or adolesc* or infan* or toddler* or bab* or young* or preschool* or "pre school*" or pre-school* or newborn* or "new born*" or new-born* or neo-nat* or neonat*)

The most recent search was conducted in May 2008.

Searching other resources

- Handsearching of respiratory care and paediatric journals
- Contact with colleagues and trialists in the field of paediatric respiratory disease
- Assessment of bibliographies of RCTs and review articles
- Contact with pharmaceutical companies manufacturing xanthines

Data collection and analysis

Selection of studies

With the exception of studies which based on the title and/or abstract are clearly not RCTs or clearly not relevant, all other citations identified above were selected for full text review.

Studies were selected, assessed for methodological quality, and data extracted by two authors independently: PS and AB. Any discordance between the two authors was discussed and resolved by consensus: if consensus could not be reached a third opinion was sought from within the Cochrane airways group. Where methodological issues were unclear, attempts were made to contact the corresponding author of the original paper to clarify these.

Data extraction and management

Data for trials were extracted and entered into Review Manager software. One author extracted the data (AB). This was checked and verified by a second author (TL or PS).

Assessment of risk of bias in included studies

We assessed the risk of bias for each study according to guidelines available in the Cochrane Handbook (Handbook 2008). We assessed the trials in terms of their risk of bias, according to the following domains:

Allocation of randomisation sequence

Concealment of allocation

Blinding

Handling of withdrawals

Jadad scores (Jadad 1996) have been retained in Characteristics of included studies, but we have not used them as the basis for analysis.

Dealing with missing data

We contacted study investigators to verify data where this could not be done from the original trial report.

Because of incomplete reporting, we imputed some of the missing data to allow inclusion of trials and to assess the sensitivity of our results with and without imputed data. When estimation was done, outcomes were reported both with and without estimation. We estimated mean differences and imputed or calculated a pooled SEM for crossover studies. We imputed SEMs for GIV data where no P value was reported, by calculating a mean difference and 95% CI based upon published SDs or SEMs for the two groups. Whilst this does not replace calculations based upon P values or raw data, these treatment effect estimates are provided by studies which did not provide a P value because they did not report a significant difference. Some SDs have been imputed in pooled estimates where >3 studies already contribute data to the overall effect estimate. For SMDs we calculated an average ratio of SD:mean as mean % and used this to estimate the missing SDs.

Where only one study has presented data in a usable form, we have entered the data in RevMan, but reported the statistics from the published paper.

Assessment of heterogeneity

Heterogeneity was tested using the I^2 statistic, which measures the extent of heterogeneity not attributable to the play of chance (Higgins 2003). Where the statistic exceeds 20% random-effects modelling was applied in order to determine whether the pooled effect estimate was altered (Higgins 2003).

Data synthesis

Data for parallel group trials are expressed as a mean difference (MD) and 95% confidence intervals.

We pooled data from crossover studies with generic inverse variance (GIV, see Handbook 2008). We used the mean differences and estimated the standard errors (SEM) based upon the published P value, or from 95% confidence intervals if available. Where these were not available, we used the published SDs for the two groups to derive a SEM. For continuous data variables (e.g. lung function) a mean difference (MD) was calculated by pooling data where a common metric was used. A standardised mean difference (SMD) was calculated where studies had measured the same outcome but with different metrics (e.g. for pooling data from different symptom scores). For GIV outcomes reporting SD units, we have expressed effect sizes in terms of the pooled standard deviation for each study (e.g. where the effect size for a given study is 0.5, this represents a mean difference between the treatment and control groups of half a pooled standard deviation as reported in that study).

For dichotomous variables (e.g. admission to hospital), an odds ratio (OR) was calculated based on the event rate data in the studies. Relative risks were also calculated as these are easier to interpret clinically. Where there were significant differences in both odds and risks, a number-needed-to-treat (benefit)((NNTB) and number-needed-to-treat (harm) (NNTH) was calculated using an online statistical package (Visual Rx - www.nntonline.net).

We pooled data using a fixed-effect model (FE), unless heterogeneity was identified.

We intended to analyse data from clinical trials under one of nine comparisons:

1. Xanthine versus placebo
2. Xanthine versus inhaled corticosteroids (ICS)
3. Xanthine versus short acting beta-2 agonists (SABA)
4. Xanthine versus cromoglycate (SCG)
5. Xanthine versus ketotifen
6. Xanthine versus leukotriene antagonists
7. Xanthine + ICS versus placebo + ICS
8. Xanthine + ICS versus long-acting beta-2 agonists (LABA) + ICS
9. Xanthine + ICS versus leukotriene antagonists (LTRA) + ICS

Sensitivity analysis

Sensitivity analyses were performed to examine the effect of: baseline asthma severity, xanthine products other than theophylline, dose and strength of inhaled corticosteroids, methodological quality, and publication bias on the primary outcome. A post-hoc analysis considered was the existence of pretrial dosing schedule.

RESULTS

Description of studies

Results of the search

A total of 1204 references were identified by searches on the Airways Group Asthma Specialised Register (searches current to May 2008). Of these, a total of 109 unique studies, reported through 118 references were retrieved.

Included studies

For the 2008 update of the review one study met the eligibility criteria of the review (Kondo 2006), giving a total of 36 included studies (41 citations) which meet the inclusion criteria of the review. For a detailed description of each included study, see Characteristics of included studies.

Design

Twenty-four studies were of a crossover design and the remaining 12 were conducted with parallel groups (Furukawa 1984; Galant 1996; Glass 1981; Kondo 2006; Meltzer 1992; Pierson 1990; Pollard 1997; Rachelefsky 1986; Reed 1998; Süssmuth 2003; Tinkelman 1993; Volovitz 1994). Nine studies had a double-dummy design (Blumenthal 1980; Carswell 1983; Chow 1989; Dusdieker 1982; Edmunds 1980; Joad 1986; Pierson 1990; Reed 1998; Volovitz 1994 for more details see 'Interventions').

Study populations

A total of 2838 participants with a diagnosis of asthma or who were described as having 'asthma symptoms' were recruited in the studies. Study samples ranged from 5 (Brenner 1988) to 747 (Reed 1998), with a median of 26. In five trials, both children and adults were recruited (Galant 1996; Joad 1986; Pierson 1990; Pollard 1997; Rachelefsky 1980). We have only used data measured in participants under the age of 18 where this has been made available. The remaining studies recruited children aged between 0 and 18 years. Studies only recruiting children under 18 months were excluded because of possible diagnostic confusion with bronchiolitis. Only two small studies (Conway 1986; Newth 1982) included some participants under 18 months: in each of these studies the mean age and variance would suggest at most a quarter of participants were below 18 months.

The definition of asthma varied between the studies according to the entry criteria. ATS-defined asthma was applied as entry criterion in six studies (Chow 1989; Joad 1986; Pierson 1990; Pollard 1997; Rachelefsky 1980; Schuller 1982). GINA was used in Kondo 2006. Lung function reversibility was used in Furukawa 1984. Requirement for treatment and lung function reversibility/obstruction defined asthma in six studies (Carswell 1983; Galant 1996; Meltzer 1992; Reed 1998; Tinkelman 1993; Süssmuth 2003). Asthma was defined in terms of symptoms in two studies (Evans 1981; Nolan 1982). In MacDonald 1979, allergic asthma was defined in terms of nasal provocation, skin prick testing and specific IgE. The definition of asthma was unclear in four studies (Edmunds 1980; Gil 1993; Rachelefsky 1986; Strang 1960). Asthma/symptoms of asthma necessitating either prophylactic or reliever medication was used in the remaining 14 studies. In one study the definition of asthma was not reported (Slater Nancy 1991).

The severity of asthma/symptoms of asthma varied between the studies from mild/moderate (Dusdieker 1982; Furukawa 1984; Galant 1996) to severe (Carswell 1983; Strang 1960) and steroid-dependent (Brenner 1988; Nassif 1981; Süssmuth 2003).

Interventions

In all studies the active intervention was an oral xanthine: in all but the oldest studies this was theophylline, but one study (Strang 1960) used choline theophyllinate and four (MacDonald 1979, Blumenthal 1980, Edmunds 1980, Evans 1981) used aminophylline. In most studies a sustained release preparation (of theophylline or aminophylline) was administered on a twice or once daily basis: a minority of older studies used non-sustained release preparations of choline theophyllinate (Strang 1960) or theophylline (Glass 1981, Hambleton 1977, Newth 1982) four times per day. Dose range is complex to summarise, as three types of strategy were used (see Characteristics of included studies). Where *fixed doses* were used for predefined age bands, doses ranged from 200 to 800 mg/day theophylline or equivalent. Where *weight-based dosages* were used these ranged from 14 to 28 mg/kg/day theophylline. The remaining studies used *individualised dosages* in a pre-study phase to achieve plasma theophylline levels within a pre-defined range: most aimed at 10-20 mcg/mL, some used 8-15mcg/mL.

The study protocols allowed for co-intervention with 'as required' short-acting beta-2 agonist (SABA). In three studies participants were recruited if they took oral/inhaled steroid medication (Brenner 1988; Nassif 1981; Süssmuth 2003). A xanthine was compared with placebo in 18 studies (Bose 1987; Carswell 1983; Conway 1986; Chow 1989; Edmunds 1980; Evans 1981; Gil 1993; Glass 1981; Levene 1986; MacDonald 1979; Pedersen 1983; Pollard 1997; Rachelefsky 1986; Reed 1998; Slater Nancy 1991; Strang 1960; Volovitz 1994; Wilson 1982). Three studies assessed the addition of xanthine to inhaled or oral corticosteroids compared with placebo (Nassif 1981; Brenner 1988; Süssmuth 2003). One study assessed the effects theophylline in comparison with an antileukotriene (montelukast) in an open label design (Kondo 2006).

The remaining studies compared a xanthine with other active agents in double-blind or double dummy studies: Xanthine versus regular SABA (N = 10: Blumenthal 1980; Chow 1989; Glass 1981; Joad 1986; Dusdieker 1982; Nolan 1982; Pierson 1990; Pollard 1997; Rachelefsky 1980; Schuller 1982); Xanthine versus ketotifen (N = one: Carswell 1983) Xanthine versus SCG (N = six: Edmunds 1980; Furukawa 1984; Glass 1981; Hambleton 1977; Newth 1982; Springer 1985); Xanthine versus ICS (N = four: Galant 1996; Meltzer 1992; Reed 1998; Tinkelman 1993).

Outcome

The primary outcome of symptom free days/nights was recorded in eight studies (Carswell 1983; Dusdieker 1982; Edmunds 1980; Pedersen 1983; Levene 1986; Wilson 1982; Chow 1989; Nolan 1982). Symptom scores were recorded in all studies. Lung function assessments were undertaken in all studies except for Conway

1986; Glass 1981; Hambleton 1977; Newth 1982; Nolan 1982 and Rachelefsky 1986.

Excluded studies

Of the studies retrieved, 73 failed to meet the eligibility criteria of the review:

Inadequate duration (28); adult population (22); assessment of the effects of treatment in exercise induced bronchoconstriction (five); not randomised (six); review articles (five); study conducted in acute asthma setting (four); wrong comparison (three). One study awaits assessment (El Kateeb 1986).

Risk of bias in included studies

An overview of the judgements for each domain of the risk of bias table is provided in Figure 1.

Figure 1. Methodological quality summary: review authors' judgments about each methodological quality item for each included study.

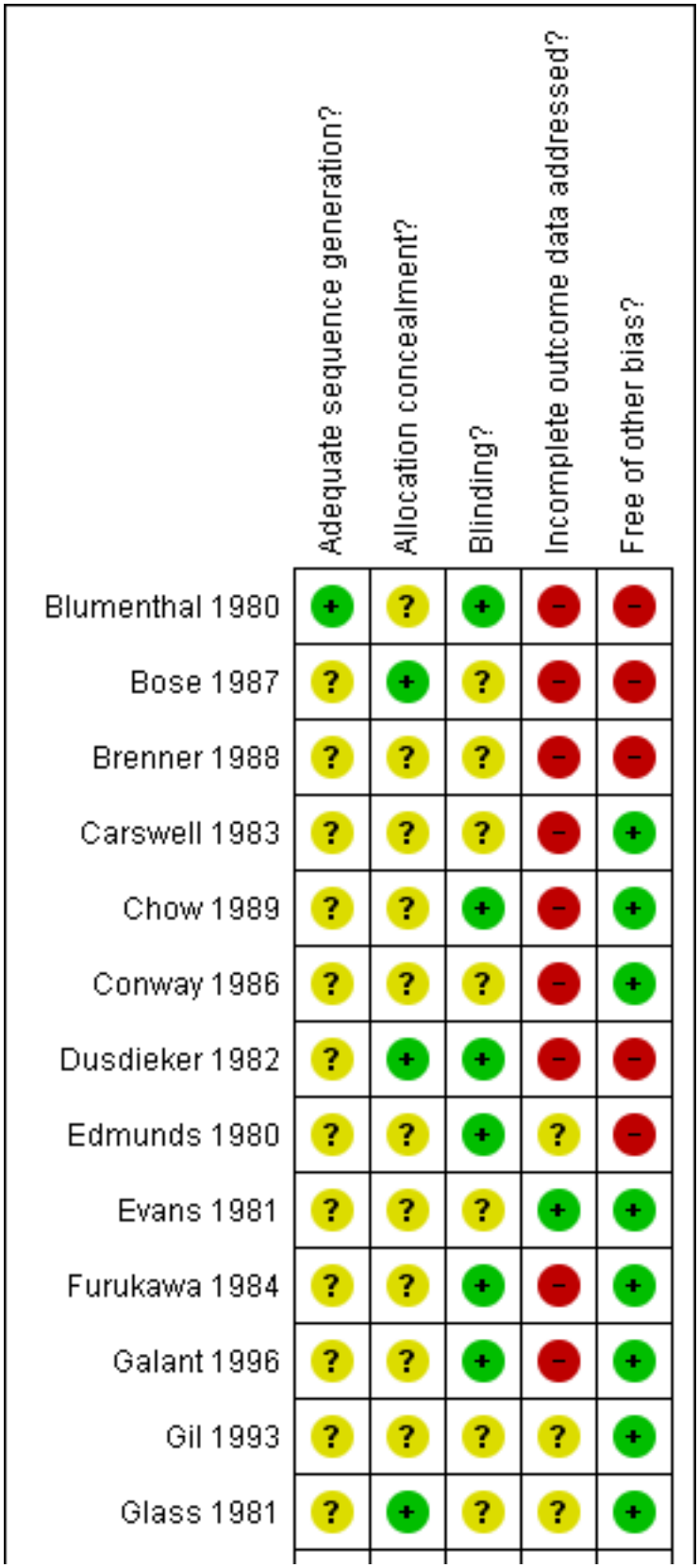


Figure 1. (Continued)

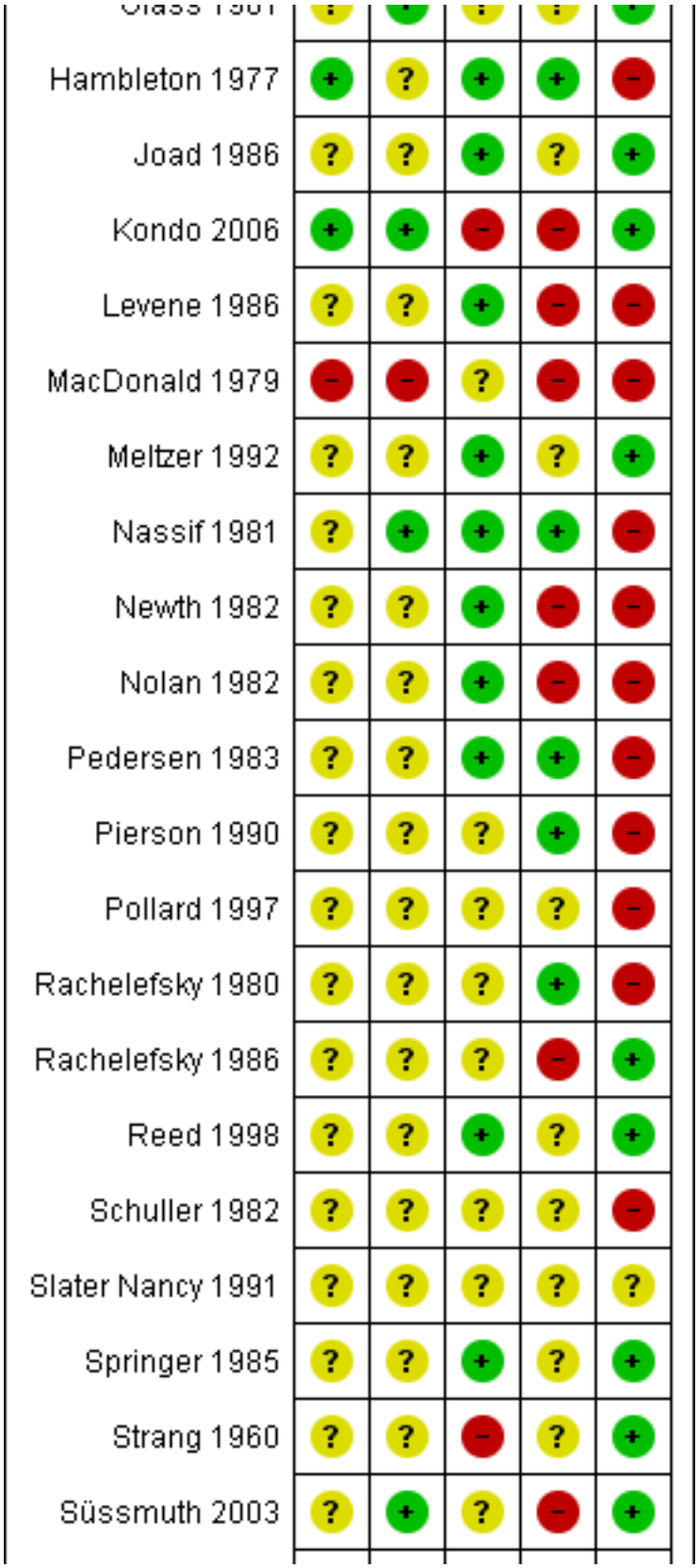
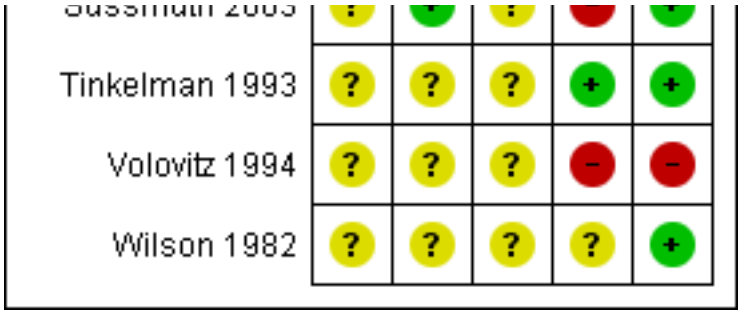


Figure 1. (Continued)



We have retained Jadad scores for each study in Characteristics of included studies.

Allocation

We judged the generation of allocation sequence to be adequate in two studies, and its concealment adequate in only six studies. The use of date of birth as a randomisation sequence in MacDonald 1979 is not sufficient to protect the study against bias. For the remainder of the trials the absence of information in the original trial reports, and the failure to obtain such information through correspondence, means that we are uncertain as to the extent to which allocation to treatment groups was free of bias.

Blinding

Information on the means by which study participants and trialists were blinded was available for 18 studies; in 16 xanthine and its comparator were identical, or a double-dummy design was used.

Pre-trial exposure to the xanthine in a number of trials (see below) may have served to unmask treatment group assignment.

Incomplete outcome data

ITT (intention to treat) analyses were reported in a limited number of parallel group studies (Galant 1996; Pierson 1990; Pollard 1997; Reed 1998; Tinkelman 1993; Süssmuth 2003), although the definition of this population was infrequently described. In seven crossover studies all participants completed both treatment arms (Chow 1989; Hambleton 1977; MacDonald 1979; Nassif 1981; Pedersen 1983; Rachelefsky 1980; Springer 1985).

Other potential sources of bias

The crossover design used in some of the crossover studies may not have adequately controlled for carry over effects. No washout phase was reported in 12 studies, and in the remainder either a washout phase was described (Bose 1987; Springer 1985), or outcomes were analysed after a threshold time point to enable washout to occur during a treatment limb (Carswell 1983; Chow 1989; Conway 1986; Glass 1981; Joad 1986; Levene 1986; MacDonald 1979; Nassif 1981; Newth 1982).

The factors limiting the validity of the studies, and potentially of the review more generally, concern the characteristics of patient populations, outcome assessment, study design and follow-up. In all the studies with the exception of Strang 1960, attempts to maintain double-blinding were made. However, in order to establish xanthine dose, a different bias was introduced. In 17 of the studies participants were exposed to a pretrial dose of xanthine, which determined the dose of xanthine based upon serum theophylline levels and/or tolerability (Blumenthal 1980; Bose 1987; Brenner 1988; Dusdieker 1982; Edmunds 1980; Hambleton 1977; Levene 1986; MacDonald 1979; Nassif 1981; Newth 1982; Nolan 1982; Pedersen 1983; Pierson 1990; Pollard 1997; Rachelefsky 1980; Schuller 1982; Volovitz 1994). Furthermore, Nassif 1981; Meltzer 1992; Brenner 1988 and Tinkelman 1993 recruited a considerable proportion of participants who had previously used a xanthine to control their asthma. In Hambleton 1977 participants were excluded if they were intolerant of xanthine.

These characteristics may affect the findings of the studies of by potentially enabling participants being able to recognise adverse effects/taste of the study drug, as well as by restricting study entry to participants who were compliant with and tolerant of the study drug. The impact of an attrition bias will most likely be to over-estimate subjective measurements of efficacy (such as symptoms and quality of life instruments) and under-estimate the instance and severity of adverse events. The numbers of participants withdrawing during the pre-dosing schedule were not adequately reported in the studies.

Effects of interventions

Comparison 01: Xanthine versus placebo

Seventeen small crossover studies conducted in children with a mixed severity of asthma contributed data to this comparison. The dosing strategy used in the studies varied. The doses given ranged from 400 mg/day (Chow 1989) to 600 mg/day (Gil 1993) and from 18 mg/kg/day (Bose 1897) to 28 mg/kg/day (Glass 1981). In several studies, the dose was titrated to keep blood theophylline levels between threshold values : 7.8 to 19.4 mcg/mL (Pedersen 1983); 10-20 mcg/ml (Edmunds 1980; Pollard 1997; Rachelefsky 1986; Volovitz 1994). Study duration was 4-12 weeks for trials contributing data to the outcomes listed.

Summary of findings for pooled estimates

There were significant differences in % symptom-free days and nights in favour of xanthine (8-13%). There were significant differences in the following outcomes in favour of xanthine: night symptoms, am PEF (5% predicted; 33 L/min), and pm PEF (4%; 26 L/min), number of puffs per day of rescue medication used (just under half a puff per patient per day). Adverse events were more frequent with xanthine when these were recorded as non-specific events. No significant differences were observed for PEF and specific adverse

events. One study reported a significant difference in favour of placebo for adjusted data on change in behaviour score.

Primary outcome: Symptom free days

(Carswell 1983; Edmunds 1980; Pedersen 1983; Nolan 1982; Wilson 1982; Levene 1986; Chow 1989; Volovitz 1994)

Symptom free 24 hour periods (outcome 01)

Significant difference in favour of xanthine: three studies, MD 7.97% [3.41, 12.53], N = 73.

Symptom free days (outcome 02)

No significant difference between xanthine and placebo: two studies, MD 12.82% [-1.96, 27.61], N = 38.

Symptom free nights (outcome 03)

Significant difference in favour of xanthine: four studies, MD 10.60% [4.17, 17.03], N = 74.

'Wheeze-free days' (outcome 04)

No significant difference: two studies, MD 4.7% [-7.54, 16.95], N = 35.

Symptom-free days: activity (outcome 05)

Chow 1989 reported no significant difference between xanthine and placebo.

'Cough-free days' (outcome 06)

No significant difference: two studies, MD 8.30% [-5.73, 22.32], N = 35.

Change in symptom free days (outcome 07)

Volovitz 1994reported that there was no significant change in the placebo group (-4%) compared with a significant change in the xanthine group (-35%, P = 0.002). Statistical tests between groups were not presented.

Carswell 1983 reported that there was a difference of 19% between xanthine and placebo for the proportion of days when symptoms were low or non-existent (P < 0.001).

Secondary outcomes

Symptom scores (Outcomes 08-14: Edmunds 1980; Conway 1986; Bose 1987; Wilson 1982; Levene 1986; Glass 1981; Nolan 1982; Chow 1989)

Symptom score: total (outcome 08): Significant difference in favour of xanthine: three studies, SMD -0.41 [-0.62, -0.19], N = 63. There was a high level of heterogeneity (I^2: 76.2%). Random-effects modelling gave a non-significant finding (-0.42 [-0.9, 0.06]). This may reflect varying sensitivity of the different symptom scales employed in the trials, or potentially divergent definitions of asthma at baseline between the studies.

Symptom score: day symptoms (outcomes 09 & 10): Significant difference in favour of xanthine: six studies, SMD -0.38 [-0.58, -0.18], N = 93. There was a moderate level of heterogeneity between the studies (I^2 36.4%). With estimated SDs for Glass 1981 (see Table 1), the level of statistical heterogeneity increased slightly (I^2 40.3%), but there was still a significant result in favour of xanthine with random effects modelling.

Symptom score: night symptoms (outcome 11 & 12): Significant difference in favour of xanthine: six studies, SMD -0.48 [-0.66, -0.29], N = 107. A pooled estimate was recalculated with SDs estimated for Glass 1981 (see Table 1). This gave a significant difference in favour of xanthine (seven studies, SMD: -0.44 [-0.62, -0.27], N = 143).

Symptom score: cough (outcomes 13): Significant difference in favour of xanthine: two studies, SMD -0.38 [-0.71, -0.05], N = 35. However, there was significant statistical heterogeneity between the two studies, and random-effects modelling gave a non-significant result (-0.44 [-0.99, 0.11]). Different scales used may have generated a difference between these studies, but more data are required for this outcome before a more meaningful exploration of heterogeneity can be undertaken.

Symptom score: activity (outcome 14): No significant difference: two studies , SMD -0.16 [-0.56, 0.24], N = 40.

Exacerbations (Outcomes 15-20: Carswell 1983; Edmunds 1980; Glass 1981; Nolan 1982; Pedersen 1983; Conway 1986; Chow 1989; Levene 1986; Strang 1960)

Hospitalisation (outcome 15): No significant difference between xanthine and placebo: five studies, OR 0.84 [0.37, 1.91], N = 84 (relative risk: 0.86 [95% CI 0.43 to 1.73].

Severe attacks of asthma (outcome 16): Edmunds 1980 reported hospitalisations and requirement for OCS as a composite outcome. Eight attacks occurred during placebo treatment, and two during theophylline treatment (P< 0.05).

Number of participants needing corticosteroids (outcome 17): No significant difference between xanthine and placebo: two studies, OR 1.00 [0.21, 4.68], N = 31, (relative risk: 1 [95% CI 0.24 to 4.15].

Days when admission to hospital necessary (outcome 18): Carswell 1983 reported a difference of -2% in favour of xanthine, but this was not significant.

Days when no additional prednisolone given (outcome 19): Carswell 1983 reported a difference of 6% in favour of xanthine, but this was not significant.

Acute attacks of asthma (outcome 20): Pedersen 1985 reported no significant difference in the average number of attacks per participant during treatment with either regimen. Strang 1960 reported no significant difference compared with placebo (difference of 0.43, t = 0.322, P>0.05).

ß2 agonist use (Outcomes 21-23) Glass 1981; Edmunds 1980; Nolan 1982; Wilson 1982; Pedersen 1983; Levene 1986; Bose 1987; Chow 1989).

Rescue ß2 agonist use (outcomes 21 & 22): We imputed missing SEMs for two studies (Glass 1981; Chow 1989). Chow 1989 reported data on ß2 agonist use for diurnal and nocturnal outcomes separately. These were added, and variance imputed by taking the SEM from confidence intervals from imputed SDs. There was a significant difference in favour of xanthine: eight studies, MD -0.41 puffs/day [-0.56, -0.26], N = 145. Although a significant degree of statistical heterogeneity was observed (I^2 64.4%), random-effects modelling did not alter the significance of the effect, MD -0.56 puffs/day [-0.93,

-0.19]. The reported effect estimate for Bose 1987 was significantly bigger than for the other studies which may reflect a different average (for example, a period of greater than one day), although this was not explicit in the published trial report. When this study was removed from the analysis the level of heterogeneity dropped to 19% (MD-0.41 puffs/day [-0.56, -0.26]).

Days when no salbutamol given (outcome 23): Carswell 1983 reported a difference of 17%, but this was not significant.

Lung function (Outcomes 24-33: Carswell 1983; Pedersen 1983; Chow 1989; Gil 1993; MacDonald 1979; Edmunds 1980; Wilson 1982; Levene 1986; Strang 1960)

Some studies reported lung function as raw values and others as % predicted. These are reported separately

FEV_1 (litres - outcome 24): Data were only available for Chow 1989 who reported no significant difference.

FEV_1 (predicted - outcome 25): Significant difference in favour of xanthine: two studies, 8.75% [0.8, 16.69], N = 31. There was a moderate degree of statistical heterogeneity. When taken account of with random effects modelling, this gave a non-significant result (9.25% [-0.17, 19.21]). The reasons for this disparity can only reliably be explored with additional data sets.

Morning PEF (predicted - outcome 26): Significant difference in favour of xanthine: three studies, 5.22% [2.91, 7.52], N = 68.

Morning PEF (L/min - outcome 27): Significant difference in favour of xanthine: two studies, 33 L/min [14.63, 52.57], N = 34.

Evening PEF (predicted - outcome 28): Significant difference in favour of xanthine: three studies, 4.05% [2.47, 5.62], N = 68.

Evening PEF (litres - outcome 29): Significant difference in favour of xanthine: two studies, 26.66 L/min [15.51, 37.81], N = 34.

Clinic PEF (outcomes 30 & 31): Individual studies reported significant differences in favour of xanthine in terms of % predicted (Pedersen 1983) and L/min (Chow 1989).

% days when PEF <50% predicted (outcome 32): Edmunds 1980 reported no significant difference between xanthine and placebo.

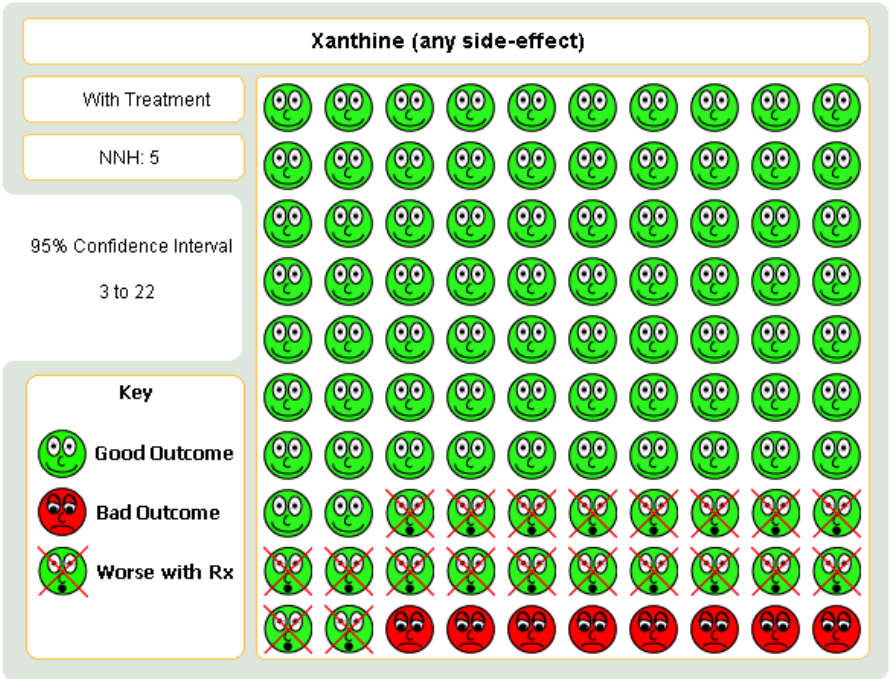
PEF - diurnal variation (outcome 33): Chow 1989 reported no significant difference between xanthine and placebo.

Side effects/tolerability (Outcomes 34-40) Bose 1987; Chow 1989; Levene 1986; Nolan 1982; Wilson 1982; Rachelefsky 1986)

Chow 1989; Wilson 1982 reported side-effect data as incidences rather than participants with adverse effects. Only limited data from Wilson 1982 were available for analysis.

Any side-effect (outcome 34): Significant difference in favour of placebo: four studies, OR 4.48 [1.65, 12.19], N = 67 (relative risk: 3.33 [95% CI 1.44 to 7.72]. This translates to a NNTH of approximately five (see Figure 2).

Figure 2. Graphic to demonstrate that for every 5 patients treated with xanthine, one patient will have an adverse event. This reflects data from trials conducted over 4-12 weeks, and assumes a baseline risk of around 8%



Headache (outcome 35): No significant difference between xanthine and placebo: two studies, OR 3.20 [0.32, 32.41], N = 33 (relative risk: 3 [95% CI 0.33 to 27.4]).

Study withdrawal (outcome 32): Due to the design of the studies reporting these data we have opted to pool only data from one parallel study with data available from the first arm of a crossover study. No significant difference between xanthine and placebo: two studies, OR 1.03 [0.28, 3.82], N = 48. (Relative risk: 1.02 [95% CI 0.47 to 2.19].

Teacher behavioural assessment score (outcome 37): Rachelefsky 1986 presented both absolute and change scores. There was a slight difference in mean baseline scores of five units. At the end of treatment, scores were non-significant when data were presented as absolute scores (P = 0.08) but were significant when presented as difference in change scores (P = 0.004). Gil 1993 reported no significant difference on cognitive and behavioural scores between theophylline and placebo.

Conners revised scales (outcome 38): Slater Nancy 1991 reported no significant difference on teacher and parent ratings.

Sleep disturbance (outcome 39): Levene 1986 reported no significant difference between xanthine and placebo.

Abdominal pain, nausea or vomiting (outcome 40): Glass 1981 reported no significant difference between xanthine and placebo.

Strang 1960 reported no adverse events related to xanthine or placebo.

Comparison 02: xanthine versus inhaled steroids

A total of four short to long term parallel group studies (4 weeks to 12 months) were identified reporting data for this group comparison (Galant 1996; Meltzer 1992; Reed 1998; Tinkelman 1993). Data from only two of these studies could be used as these were conducted exclusively in children (Meltzer 1992; Tinkelman 1993). Galant 1996 and Reed 1998 only reported data for mixed child and adult populations, and it was impossible to separate the data. Doses in Tinkelman 1993 were adjusted to achieve theophylline level 8 to 15 mcg/ml, and in Meltzer 1992 doses were titrated to achieve theophylline levels of between 8 and 18 mcg/ml. For details of inhaled steroid doses used see 'Table of included studies'.

Summary of pooled findings

Although no data were reported for symptom-free days, there was evidence that inhaled steroids were more effective than xanthine in preventing exacerbations (NNTB 10), and was more tolerable in terms of nausea (NNTH 8) and headache (NNTH 8). No significant differences were observed in lung function, rescue medication usage, tremor and study withdrawal.

Primary outcome: Symptom free days

No data were reported for this outcome in the studies.

Secondary outcomes

Symptoms (Outcome 1-6; Tinkelman 1993; Meltzer 1992)

Symptom slope (Outcome 01): Tinkelman 1993 (N = 150) reported that the mean slope of symptom change was greater in those treated with BDP compared with those treated with xanthine (P < 0.001).

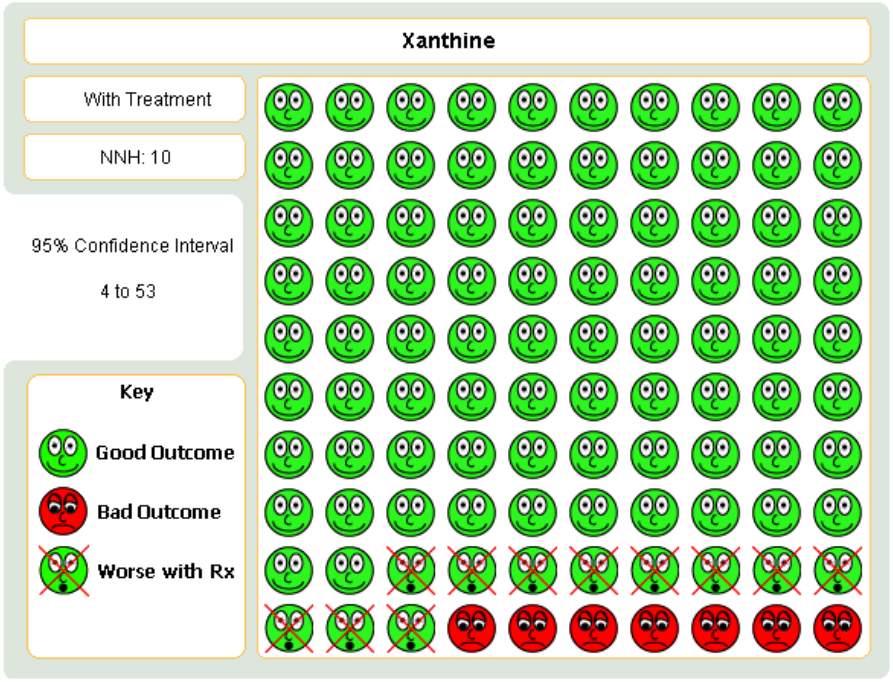
Symptoms of cough, wheeze, activity tolerated, shortness of breath and nocturnal symptoms (outcomes 02-06): Meltzer 1992 (N = 59) reported that BDP-treated participants had fewer symptoms compared with xanthine treated participants (P </= 0.006).

Participants helped by medication (outcome 07): Meltzer 1992 reported that fewer participants treated with theophylline were helped by their medication compared with BDP (19/39 versus 29/37, P = 0.001).

Exacerbations (Outcomes 08: Meltzer 1992; Tinkelman 1993)

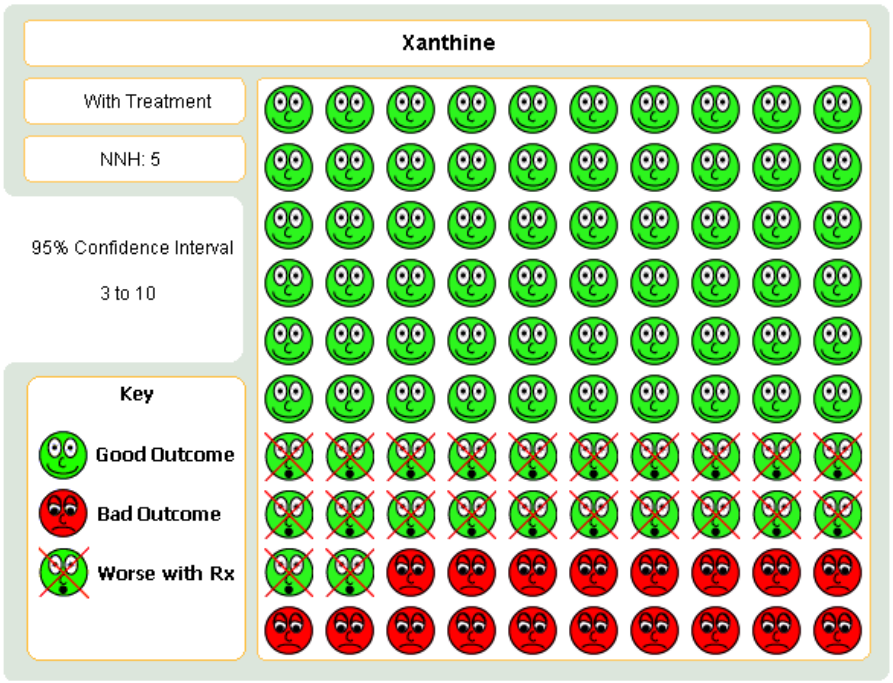
Participants with more than one exacerbation (outcome 08): In spite of slightly different definitions of exacerbation/hospitalisation, there was a significant effect in favour of ICS: two studies, OR: 2.87 [1.30, 6.36], N = 271. (relative risk 2.44 [95% CI 1.23 to 4.85]). This translates to a NNTB of approximately 10 (see Figure 3).

Figure 3. Graphic to demonstrate that compared with inhaled steroids of between 100 and 400mcg/d in mild to moderate asthma patients, an additional 10 patients will experience an exacerbation of asthma out of every 100 treated. The studies were conducted over a period of 1 to 3 months, and assume a baseline risk of approximately 7%.



Participants requiring oral steroid treatment (outcome 09): There was a significant difference in favour of ICS: two studies, OR: 3.10 [1.78, 5.41], N = 267 (relative risk 2.26 [95% CI 1.49 to 3.41]). This translates to a NNTB of 5 (see Figure 4).

Figure 4. Graphic to demonstrate that out of every 100 patients treated with xanthine instead of inhaled steroids at a dose of between 100 and 400mcg/d in mild to moderate asthma patients, 20 more will require a course of coritcosterods over a period of between 1-3 months. This assumes a baseline risk of 18%.



Additional systemic steroid use (outcome 10): Tinkelman 1993 reported that there was a significant difference in favour of BDP in terms of the amount of systemic steroid used of 65.5 mg (P = 0.002).

Rescue medication use (Outcome 11: Meltzer 1992; Tinkelman 1993)

Participants requiring additional ß2 agonist (outcome 11): No significant difference between xanthine and ICS: two studies, OR 1.61 [0.92, 2.82] (relative risk 1.21 [95% CI 0.97 to 1.5]).

Lung function (Outcomes 12-15: Meltzer 1992; Tinkelman 1993)

FEV_1 (% predicted - outcome 12): There was no significant difference in post-bronchodilator (BD) FEV_1: two studies, MD-2.54% [-6.85, 1.77], N = 321.

Tinkelman 1993 and Meltzer 1992 reported no significant difference in PEF as daily (outcome 13) or am average (outcome 14), or in FEF_{25-75} (outcome 15).

Side-effects and tolerability (Outcomes 16-20: Meltzer 1992; Tinkelman 1993)

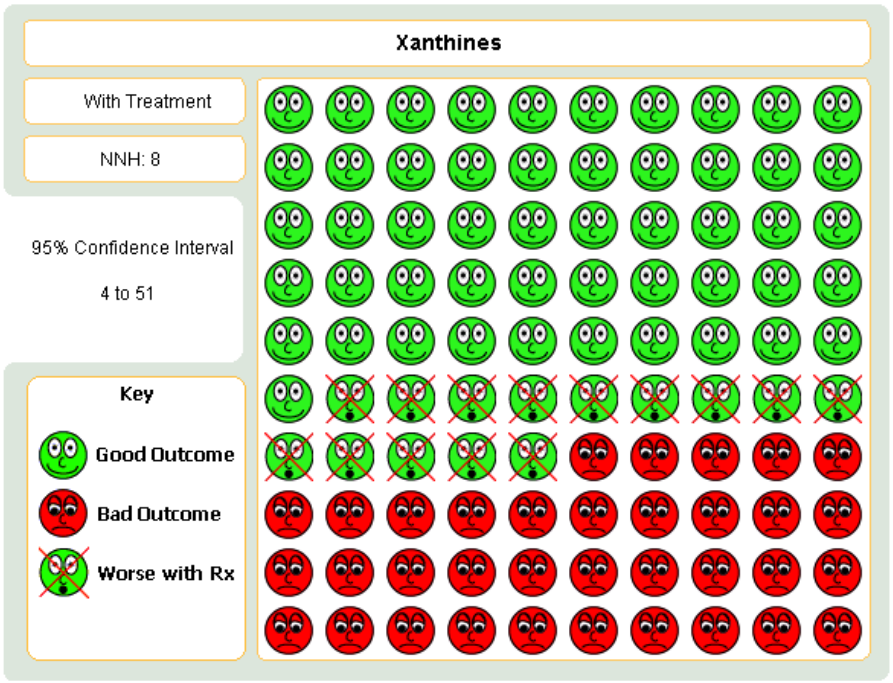
Growth rate (outcome 16): Tinkelman 1993 reported that growth rate overall was significantly in favour of xanthine when expressed as mean difference between observed and predicted growth rates over the treatment period (Xanthine: 0.4 cm versus steroid: -0.7 cm; 48 weeks, P = 0.001).

Behaviour checklist (outcome 17): Tinkelman 1993 reported no significant difference on a child behaviour checklist scale.

Headache (outcome 18): Fewer participants suffered from headaches when treated with ICS: two studies, OR 1.76 [1.09, 2.83], N = 286 (relative risk 1.39 [95% CI 1.05 to 1.84]). This translates to a NNTH of 8 (see Figure 5).

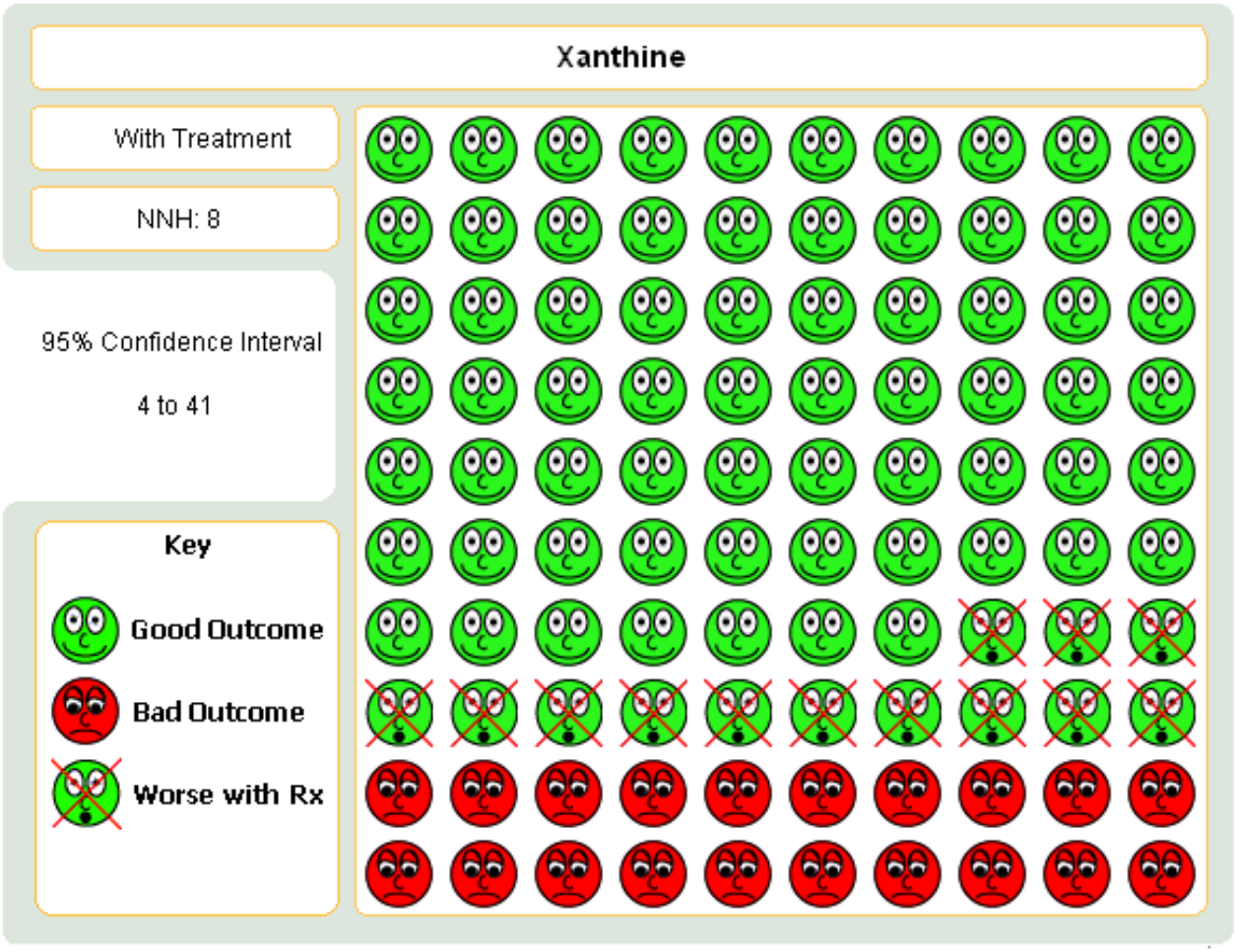
Tremor (outcome 19): No significant difference between xanthine and ICS: two studies, OR 1.48 [0.53, 4.14], N = 286 (relative risk 1.45 [95% CI 0.56 to 3.74]). There was a high level of heterogeneity (I2 80.5%). 85% participants in Meltzer 1992 were taking a xanthine prior to the study, whereas 42% participants in Tinkelman 1993 had previously taken a xanthine to control their asthma. This difference between these populations in terms of their tolerance of the study drug at study entry, may account for the variation between the studies.

Figure 5. Graphic to demonstrate that out of every 100 patients treated with xanthine instead of inhaled steroids at a dose of between 100 and 400mcg/d in mild to moderate asthma patients, 14 more will experience headache over a period of between 1-3 months. This assumes a baseline risk of 35%.



Nausea (outcome 20): There was a significant and consistent effect in favour of ICS compared with xanthine: two studies, OR 1.98 [1.16, 3.40], N = 286 (relative risk 1.65 [1.11, 2.47]). This translates to a NNTH of 8 (Figure 6)

Figure 6. Graphic to demonstrate that for every 100 patients treated with xanthines rather than BDP (between 100-400mcg/d) over a period of 1-3 months, 8 would need to be treated in order for one patient to develop nausea. This assumes a baseline risk of around 20%.



Study withdrawal (Outcome 21-24: Meltzer 1992; Tinkelman 1993)

Withdrawal from study (outcome 21): No significant difference: OR: 1.42 [0.82, 2.47] (relative risk 1.31 [95% CI 0.85 to 2]).

Withdrawal due to lack of benefit (outcome 22): No significant difference: two studies, OR 1.01 [0.54, 1.90] (relative risk 1.01 [95% CI 0.63 to 1.62])

Withdrawal due to adverse effects (outcome 23): No significant difference: two studies, OR 1.60 [0.37, 6.80] (relative risk 1.58 [95% CI 0.38 to 6.48]).

Withdrawal due to exacerbation (outcome 24): Meltzer 1992 reported a significant difference in favour of BDP (Xanth: 7/39; BDP: 1/37, P < 0.05).

Comparison 03: Xanthine versus regular short-acting beta-2 agonists

Ten crossover studies contributed data to this outcome. Dosing strategies varied between the trials. In six of these studies theophylline levels were maintained between 10-20 mg/ml. Fixed doses of xanthine were assessed in Chow 1989 (400 mg/day). Glass 1981 assessed the effects of xanthine given at 6-mg/kg per dose qds (i.e. around 28 mg/kg/day). Study duration varied between four weeks (Chow 1989; Dusdieker 1982; Joad 1986; Schuller 1982) and 12 weeks (Pollard 1997). For details of SABA doses used, see 'Table of Included Studies'.

Summary of pooled findings

No data could be pooled for the primary outcome. Symptom scores and rescue beta-2 agonist use did not differ significantly between xanthine and beta-2 agonists, although hospitalisations were less frequent in participants treated with short-acting beta-2 agonist (NNTH 7). Headache was more frequent with xanthine (NNTH 5), but tremor was more frequent with beta-2 agonist (NNTH 4).

Primary outcome: Symptom free days

(outcomes 1-5; Dusdieker 1982; Chow 1989; Nolan 1982)

Symptom free days (outcome 01)

No significant difference: three studies, 5.7% [-2.11, 13.51], N = 71.

Symptom free days: day wheeze (outcome 02)

No significant difference: two studies, -4.2% [-16.02, 7.62], N = 35.

Symptom free days: activity (outcome 03)

Chow 1989 reported no significant difference between xanthine and beta-2 agonist, but presented no usable data.

Symptom free days: cough (outcome 04)

No significant difference: two studies, 3.34% [-10.23, 16.91], N = 35.

Symptom free days: cough (outcome 05)

No significant difference: two studies, 0.2% [-13.61, 14], N = 35.

Secondary outcomes

Symptoms (outcomes 6-12; Rachelefsky 1980; Schuller 1982; Chow 1989; Nolan 1982)

Symptom score: total (outcome 06): Rachelefsky 1980 reported a significant difference in total symptoms in favour of xanthine (P=0.05).

Symptom score: day wheeze (outcome 07): No significant difference: four studies, SMD -0.09 [-0.31, 0.14], N = 75. Although a moderate degree of heterogeneity was observed (I^2 52.5%), random-effects modelling did not alter the direction of the effect.

Symptom score: shortness of breath (outcome 08): Rachelefsky 1980 reported no significant difference between xanthine and beta-2 agonist (P = 0.22).

Symptom score: daytime chest tightness (outcome 09): Rachelefsky 1980 reported no significant difference between xanthine and beta-2 agonist (P = 0.11)

Symptom score: activity (outcome 10): Chow 1989 reported no significant difference between xanthine and beta-2 agonist.

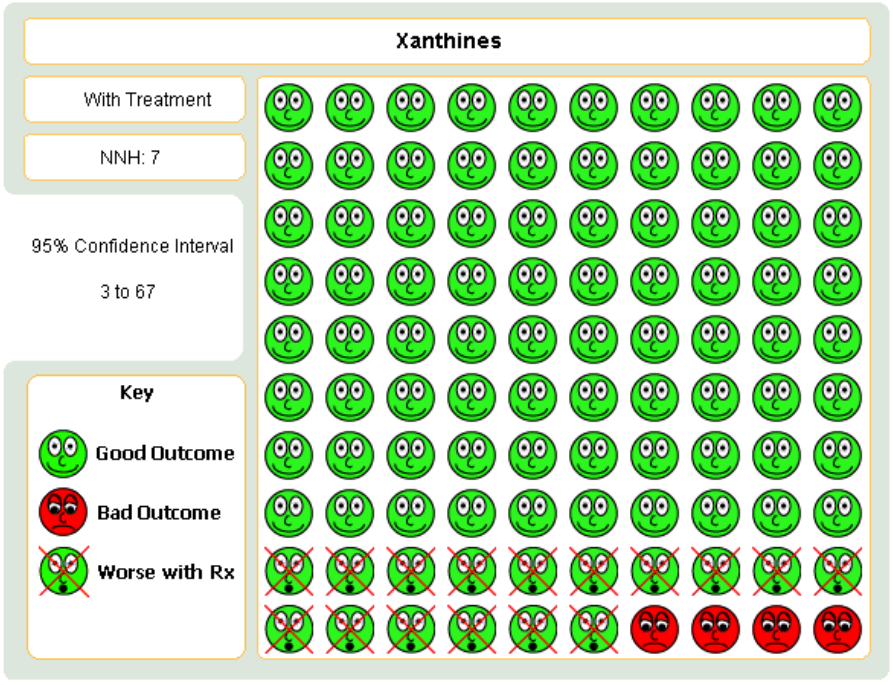
Symptom score: cough (outcome 11): Significant difference in favour of xanthine: three studies, SMD -0.27 [-0.55, 0], N = 55.

Symptom score: night symptoms (outcome 12): No significant difference: four studies SMD -0.20 [-0.43, 0.03], N = 75.

Exacerbations (outcomes 13-16; Dusdieker 1982; Rachelefsky 1980; Chow 1989; Nolan 1982; Schuller 1982)

Hospitalisations/ER treatment (outcome 13): There was a significant effect in favour of regular beta-2 agonists: three studies, OR 6.00 [1.40, 25.60], N = 55**.** (RR: 4.6 [1.26, 16.84]). This translates to a NNTH of around seven (see Figure 7).

Figure 7. Graphic to demonstrate that for every 100 patients treated with xanthines instead of regular short acting beta-agonists alone, 16 more patients will suffer an exacerbation of their asthma leading to hospitalisation/ER treatment. This is based on studies of between 4 and 12 weeks duration, and assumes a stable baseline risk of 4%.



Mean acute attacks of asthma (outcome 14 & 15): Rachelefsky 1980 reported a significant difference in favour of xanthine on daytime attacks of asthma (P < 0.04), but not for night attacks (P = 0.9).

Number participants requiring oral steroids (outcome 16): One study reported data for this outcome (N = 32, Dusdieker 1982). There was a significant difference in the number of participants who required steroids during one phase of treatment (data on participants requiring steroids in both phases were not analysed - N = four): Xanthine phase: 1/32; beta-2 agonist phase: 10/32, P < 0.02.

Additional beta-2 agonist use (outcomes 17 & 18; Nolan 1982; Rachelefsky 1980; Chow 1989)

Additional beta-2 agonist dose per day (outcome 17): No significant difference between xanthine and beta-2 agonist: two studies: MD-0.38 puffs per day [-0.93, 0.18], N = 44.

Additional beta-2 agonist - mean weekly score (outcome 18): Nolan 1982 reported no significant difference between xanthine and beta-2 agonists.

Lung function (outcomes 18-23; Chow 1989; Dusdieker 1982; Rachelefsky 1980)

FEV_1 (outcome 19): Chow 1989 reported no significant difference between xanthine and beta-2 agonists.

FEV_1 (outcome 20): Dusdieker 1982 reported no significant difference between xanthine and beta-2 agonists.

FEV_1 (parallel group/first arm data; outcome 21): Rachelefsky 1980 reported no significant difference between xanthine and beta-2 agonists.

Morning PEF (outcome 22): Significant difference in favour of xanthine: two studies, 18.13 L/min [3.59, 32.68], N = 44.

Evening PEF (outcome 23): Significant difference in favour of xanthine: two studies, 8.66 L/min [1.71, 15.6], N = 44.

Clinic PEF predicted (outcome 25): Dusdieker 1982 reported no significant difference between xanthine and beta-2 agonists.

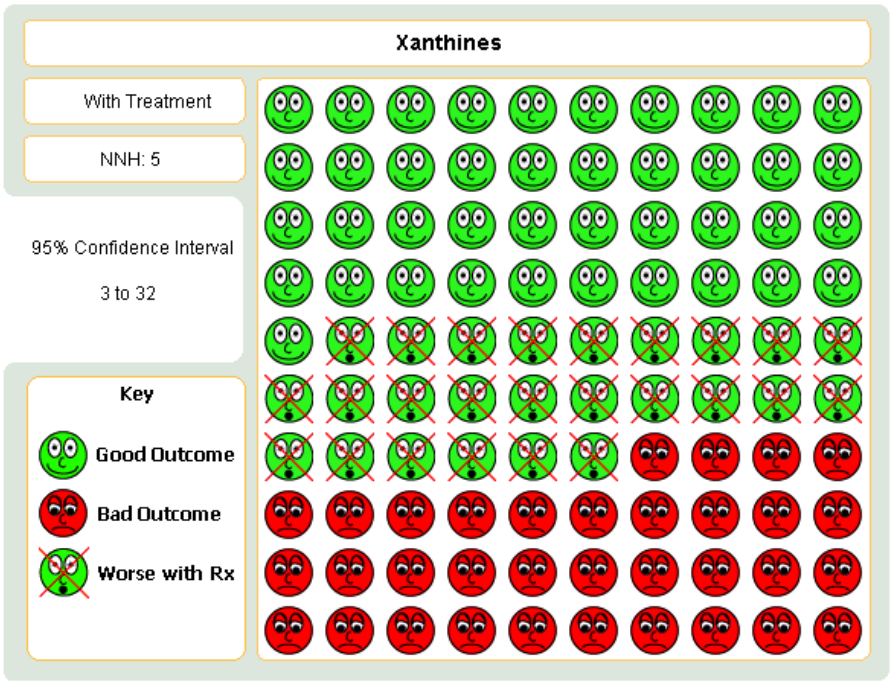
Chow 1989 reported no significant difference in diurnal variation and clinic PEF (outcome 24 & 26). Dusdieker 1982 reported a significant difference in RV/TLC in favour of xanthine (P = 0.02; outcome 27).

Side effects and tolerability (outcomes 28-38; Dusdieker 1982; Nolan 1982; Schuller 1982; Chow 1989)

Schuller 1982 reported no side-effects throughout the study. Nolan 1982 reported no significant differences between xanthine and beta-2 agonists for any adverse events (outcome 28).

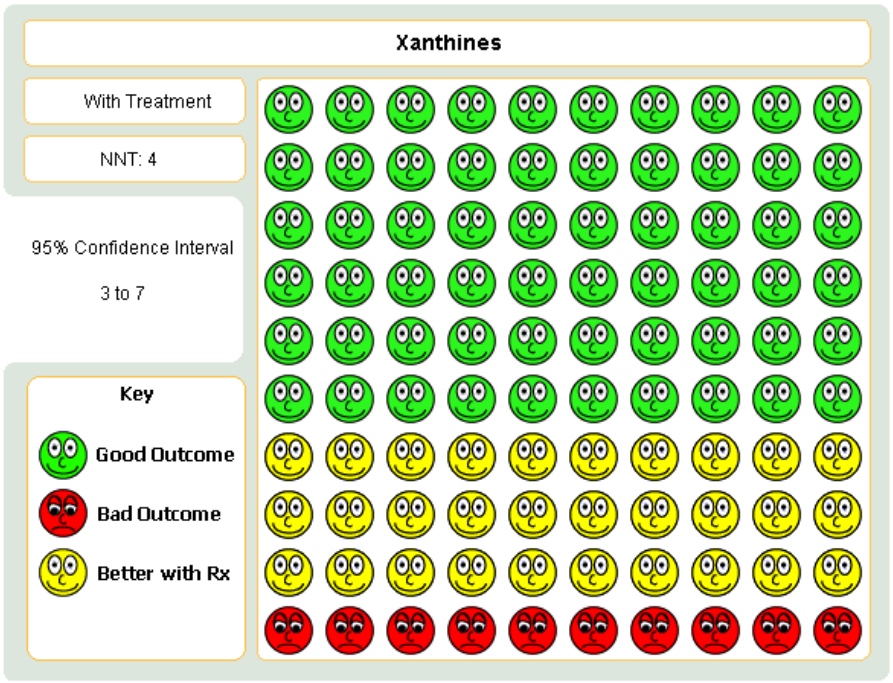
Headache (outcome 32): There was a significant effect in favour of beta-2 agonist: two studies, OR 2.74 [1.15, 6.55], N = 53 (relative risk 1.61 (95% CI 1.06 to 2.44). This translates to a NNTH of around 5 (see Figure 8).

Figure 8. Graphic to demonstrate that for every 100 patients treated with xanthines instead of regular short acting beta-agonists alone, 25 more patients will suffer headache. This is based on studies of between 4 and 8 weeks duration, and assumes a stable baseline risk of 34%.



Tremor (outcome 35): There was a significant effect in favour of xanthine: two studies, OR 0.17 [0.06, 0.50], N = 53 (relative risk 0.3 [95% CI 0.14 to 0.65]). This translates to a NNTB of around 4 (see Figure 9).

Figure 9. Graphic to demonstrate that for every 100 patients treated, 30 fewer patients would experience tremour with xanthines compared with regular tretament with SABA alone. This is based upon studies of between 4-8 weeks duration, and assumes a stable baseline risk of 40%.



Dusdieker 1982 reported no significant differences between xanthine and placebo on the remaining outcomes: nausea (outcome 34); abdominal pain (outcome 25); diarrhoea (outcome 26); vomiting (outcome 27); nervousness (outcome 29); insomnia (outcome 30), palpitations (outcome 32), bad taste (outcome 33).

Chow 1989 reported adverse effects as events rather than as participants experiencing events and so data could not be pooled with those from other studies. Side-effects occurred more frequently in the beta-2-agonist and xanthine groups compared with placebo, but no analysis was made comparing beta-2 agonist with xanthine.

Comparison 04: Xanthine versus sodium cromoglycate (SCG)

Six crossover studies contributed data on 161 children to this group comparison. The studies were conducted over short to medium term durations (4-12 weeks). Dosing strategies for studies which are not reported elsewhere were (target plasma theophylline levels) - Furukawa 1984: 10-15 mcg/ml; Newth 1982 and Springer 1985: 10-20 mcg/ml. For doses of SCG used, see 'Table of Included Studies'.

Summary of pooled findings

No significant difference in % symptom-free days. No differences in symptoms and exacerbations. There were fewer instances of gastro-intestinal side-effects in children given SCG (NNTH 6).

Primary outcome: Symptom free days

Edmunds 1980; Hambleton 1977; Newth 1982; Springer 1985

Percentage of symptom free days (outcome 01)

No significant difference between xanthine and SCG: four studies, mean difference -1.27% [-6.64, 4.10], N = 97. There was a high level of heterogeneity (80.9%). This resolved partially when Hambleton 1977 was removed from the analysis. This resulted in a significant difference in favour of SCG of -7.88% [-14.47, -1.29] (I^2 52.7%). The principal difference between Hambleton 1977 and the other studies was that participants were included if they were tolerant of xanthine at baseline. Whilst xanthines had been taken by varying proportions in the remaining studies prior to study entry, Hambleton 1977 recruited a tolerant and therefore a potentially more biased sample of children. However, such a characteristic may only partly explain between-study variation as the remaining level of heterogeneity remained moderate.

Secondary outcomes

Symptoms (outcome 02 & 03: Edmunds 1980; Springer 1985; Furukawa 1984)

Symptom score (outcome 02): Significant difference in favour of xanthine: two studies, SMD: 0.42 [0.12, 0.71], N = 43. Significant heterogeneity was observed (I^2 81.4%). When random-effects modelling was applied, the effect was non-significant 0.29 [-0.46, 1.04]. The variance in Edmunds 1980 was much narrower

than in Springer 1985 and this may be attributable to the different symptom score used, or a more homogenous sample of participants. A formal exploration of heterogeneity would not be useful as the differences between the studies may not represent true heterogeneity, in the absence of additional studies.

Improvement in asthma severity (outcome 03): Furukawa 1984 reported that 11/18 and 14/22 had a subjective improvement in asthma severity by the end of the study (no statistical test undertaken).

Exacerbations (outcomes 4-6: Glass 1981; Newth 1982; Edmunds 1980; Hambleton 1977; Furukawa 1984)

Hospitalisation (outcome 04): No significant difference: two studies, OR 1.71 [0.22, 13.46], N = 42.

Severe attacks of asthma (outcome 05): A different measurement of acute asthma precluded pooling data with the studies above. Edmunds 1980 reported two severe attacks of asthma (as either hospitalisation or requirement for OCS at home) in two participants for each treatment group. No statistical test was undertaken between active treatment groups.

Number of participants requiring steroids (outcome 06): Glass 1981 reported that no events occurred on either treatment. Hambleton 1977 reported no significant difference.

Additional ß2-agonist use (outcomes 7: Edmunds 1980; Glass 1981; Hambleton 1977; Springer 1985)

Additional ß2-agonist use (outcome 7): Data for this outcome were obtained from published individual scores (Hambleton 1977), from published means with from SEMs estimated from previous outcomes (Edmunds 1980; Glass 1981), and from published means with an average pooled SD based upon the other studies (Springer 1985). No significant difference: four studies, -0.06 puffs per day [-0.15, 0.04], N = 87.

Lung function (outcomes 08-13: Hambleton 1977; Springer 1985; Edmunds 1980; Furukawa 1984)

Daily PEF (% predicted - outcome 08): No data were available for meta-analysis. Hambleton 1977 and Springer 1985 reported no significant difference between xanthine and SCG in the studies.

Am PEF (% predicted - outcome 09): Edmunds 1980 reported identical values for xanthine and SCG.

Pm PEF (% predicted - outcome 10): Edmunds 1980 reported identical values for xanthine and SCG.

% days when PEF <50% predicted (outcome 11): Edmunds 1980 reported no significant difference between xanthine and SCG.

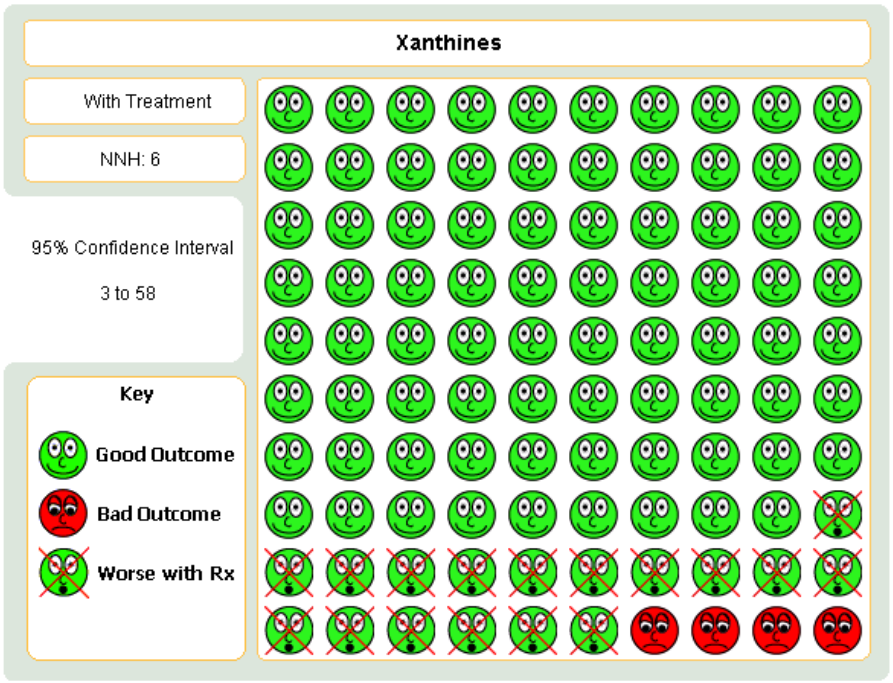
Number of participants with reduction in bronchial reactivity (outcome 12): Furukawa 1984 reported no significant difference between xanthine and SCG.

Side effects and tolerability (outcomes 13-16: Hambleton 1977; Newth 1982; Furukawa 1984)

Gastro-intestinal side effects (outcome 13): There was a significant difference in favour of SCG versus xanthine: two studies, OR: 6.28 [1.46, 27.08], N = 54 (relative risk 4.6 [95% CI 1.27 to 16.67]). This translates to a NNTH of around six (see Figure 10)

Restlessness & Insomnia (outcomes 14 & 15): Newth 1982 reported that six and five participants reported restlessness and insomnia respectively when treated with xanthine compared with none on SCG. These side-effects were described as transitory in most children.

Figure 10. Graphic to demonstrate that for every 100 patients treated 17 more patients treated with xanthines will experience GI symptoms comapred with patients treated with sodium cromoglycate. This reflects data drawn from studies conducted between 4-8 weeks, and assumes a stable baseline risk of 4%



Study withdrawals (outcome 16): Furukawa 1984 reported five withdrawals from the xanthine group and one from the SCG group. No statistical analysis was reported.

Comparison 05: Xanthine versus ketotifen

One study reported data for this comparison (Carswell 1983). Xanthine led to 11% fewer days on which symptoms were low over ketotifen, but no statistical test of significance were reported for this difference. Similarly, xanthine treatment led to 17% fewer days on which no salbutamol was used, but no statistical test of significance were reported for this difference. Hospital admission was necessary on 2% more days with xanthine compared with ketotifen, but no statistical test of significance were reported for this difference. Ketotifen led to a difference of 5% days when no additional oral steroids were required, but no statistical test of significance were reported for this difference. Peak flow was greater with xanthine by 10% compared with Ketotifen, but no statistical test of significance were reported for this difference.

Comparison 06: Xanthine versus leukotriene antagonists

No studies were identified which assessed this comparison.

Comparison 07: Xanthine versus placebo as add-on therapy to ICS

Three studies reported data for this comparison (Brenner 1988; Nassif 1981; Süssmuth 2003). However, limited data could be pooled due to divergent outcome assessment and different study design (Nassif 1981 and Brenner 1988 were crossovers; Süssmuth 2003 was a parallel study). Brenner 1988 recruited participants who were on both oral and inhaled steroids. Participants in the other studies were overall less severe, but were treated with inhaled steroids. A subgroup of participants in Nassif 1981 were treated with oral steroids.

Dosing protocols differed between the studies. Brenner 1988 administered xanthine to achieve serum levels of 10-20 mcg/ml; Nassif 1981 achieved levels of 8 to 24 mcg/ml, titrated the dose of xanthine based upon the response to therapy in participants and Süssmuth 2003 gave xanthine as 20 mg/kg/day (up to maximum of 600 mg/day). For doses of ICS used, see 'Table of Included Studies'.

All data have been entered, but no meta-analytical statistical tests of significance have been applied. Data from these studies are reported narratively.

Primary outcome

Symptom free days (outcome 01, Nassif 1981)

Percentage of symptom free days (outcome 01)

Nassif 1981: Xanth: 71% (SEM 6); placebo: 50% (SEM 5), N = 21. P < 0.01.

Secondary outcomes

Symptoms (outcome 02-04, Brenner 1988; Süssmuth 2003)

Symptoms (outcome 02): Brenner 1988 reported a significant group difference in favour of xanthine treatment of 1.48 (P = 0.006).

Daytime and nocturnal symptoms (outcome 03 & 04): Süssmuth 2003 reported no group difference in daytime and nocturnal symptom scores.

Lung function (outcomes 5-16, Nassif 1981; Süssmuth 2003)

Statistical analyses from Nassif 1981 could not be used as they referred to pooled effect estimates between ICS and OCS dependent asthmatics. The means and SEMs are reported here for completeness.

am & pm PEF (% predicted - outcomes 05 & 06): Nassif 1981: am PEF: Xanth: 105 (SEM 6); placebo: 100 (SEM 6); pm PEF: Xanth: 107 (SEM 6), placebo: 103 (SEM 5), N = 21.

Clinic PEF (% predicted - outcome 07: pre-BD; outcome 08: post-BD): Nassif 1981: Pre-BD: Xanth: 105 (SEM 5), placebo: 102 (SEM 8); post-BD: Xanth: 109 (SEM 6); placebo: 104 (SEM 7), N = 18. *Outcome 09*: Süssmuth 2003 reported a significant group difference (no mean given, CI: 1.6, 16.94 L/min, P = 0.02, N = 36) in favour of xanthine.

FEV1 (% predicted - outcome 10: pre BD; outcome 11: post BD): Pre-BD Nassif 1981: Xanth: 88 (SEM 4); placebo: 80 (SEM 4), N = 18; post-BD: Nassif 1981: Xanth 94 (SEM 4), placebo 91 (SEM 3), N = 18; Süssmuth 2003: Xanth: 85.8 (SD 15.1); placebo: 89.6 (11.6), P = 0.7, N = 36.

FVC (outcomes 12: pre-BD; 13: post-BD): Nassif 1981: Pre-BD: Xanth: 106 (SEM 3), placebo: 100 (SEM 4), N = 18; post-BD: Xanth: 110 (SEM 3), placebo: 106 (SEM 3), N = 18. No P values reported.

FEF_{25-75} (% predicted - outcome 14: pre-BD; outcome 15: post-BD): Pre-BD: Xanth: 64 (SEM 6); placebo: 54 (SEM 6), N = 18; post-BD: Xanth: 73 (SEM 7); placebo: 70 (SEM 8), N = 18. No P values reported.

Residual volume (% predicted - outcome 16): Nassif 1981: Xanth: 168 (SEM 16); placebo: 182 (SEM 16), N = 18. No P values reported.

Exacerbations (outcome 17, Nassif 1981)

Statistical analyses from Nassif 1981 could not be used as they referred to pooled effect estimates between ICS and OCS dependent asthmatics.

Requirement for additional prednisolone (outcome 17): Nassif 1981: Xanth: 1/21; placebo: 6/21 (OCS required by participants during both treatments: N = 1).

Additional medication usage (outcome 18 & 19 Brenner 1988; Süssmuth 2003)

Beta-2 agonist use (outcome 18): Significant heterogeneity existed between the two crossover studies (Brenner 1988 and Nassif 1981) and data were not pooled due to the extreme level of statistical variation (I^2 81.5%). Random Effects modelling gave a non-significant result even though the lower CI of each study was clear of the line of no difference. The smaller study by Brenner 1988 (significant difference of 2.25 puffs per day less with xanthine treatment (P = 0.009)) recruited five participants none of whom were able to complete the placebo phase. They were on both inhaled and oral steroids, and may have been an especially severe subgroup of patients. The larger study by Nassif 1981 (mean difference of 0.5 puffs per day in favour of xanthine (P < 0.01)) recruited 33 participants who were on inhaled steroid therapy, but who were not as 'brittle' as the participants in Brenner 1988. Süssmuth 2003 reported no significant difference (absolute scores: 5.8 puffs/week in Xanthine treated participants versus 3.1 puffs per week in placebo). The effect of xanthine treatment on medication usage in severe paediatric asthma warrants further investigation before firmer conclusions can be drawn.

Daily oral steroid consumption (outcome 19): Brenner 1988 reported a mean difference of 20.7 mg per day less in favour of xanthine compared with placebo (P = 0.03).

Withdrawals (outcome 20 Süssmuth 2003)

Withdrawals (outcome 20): Süssmuth 2003 reported that three participants withdrew from the study - one from placebo and two from xanthine. No P value reported.

Side-effects and tolerability outcome 21, Nassif 1981; Süssmuth 2003)

Drug tolerability was not reported in a manner conducive to data extraction and entry in Nassif 1981. Overall side effects were described as mild, transient and occurred when treatment was switched from placebo to xanthine. Exposure to the study drug pre-randomisation may account for the apparent infrequency and mildness of events in Nassif 1981. Süssmuth 2003 reported that one participant from the xanthine group withdrew due to nausea and vomiting, but that no other side effects were reported (outcome 21).

Comparison 08: Xanthine versus LABAs as add on to ICS

No studies were identified which assessed this comparison.

Comparison 09: Xanthine versus leukotriene antagonists as add on to ICS

One study was identified which assessed this comparison (Kondo 2006). The study did not measure the primary outcome of the review, and reported statistically significant differences between xanthine and antileukotriene (montelukast) in PEF as change scores, but gave only numerical data for end of treatment values which were not statistically significant.

DISCUSSION

We have assembled evidence from 36 studies, recruiting a total of 2838 participants with varying severities of asthma in studies conducted between 1960 and 2006.

The studies fall into two distinct categories from a therapeutic point of view: those in which use of xanthines as a *primary preventer* were examined (Comparisons 01 to 05) and those in which xanthines as *add-on preventer* (to steroids) were examined (Comparison 06). In summary, as primary preventer there was evidence of clear benefit in terms of symptoms and lung function, with some inconclusive evidence of side-effects. However, xanthines as primary preventer were less effective than inhaled steroids. As an additional preventer to inhaled and/or oral steroids, no firm conclusions could be reached.

The studies comparing xanthines with placebo in children (comparison 01, 17 studies) showed clear evidence of benefit on the primary outcome measure, symptom-free days, and on a variety

of the secondary outcome measures, including night symptom scores, rescue beta-2 agonist use, and lung function. The size of these effects was in the order of 8-13% fewer days/nights without symptoms, 5% predicted am PEF and 4% predicted pm PEF. There was evidence of increased side-effects overall compared to placebo (NNTH 5), but no significant increase in the incidence of any specific side-effect, whether headache, gastrointestinal disturbance or psychomotor performance. Our findings are in agreement with a previous meta-analysis (Stein 1996), which found little evidence of behavioral and cognitive effects of theophylline and caffeine in therapeutic doses.

Only two studies compared xanthines with inhaled steroids specifically in children (Comparison 02), neither reporting data for symptom-free days. Inhaled steroids were more effective than xanthine in preventing exacerbations (NNTH 10) and more tolerable in terms of nausea (NNTH 8) and headache (NNTH 8). No significant differences were observed in lung function or rescue medication usage.

Ten studies compared xanthine with regular short-acting beta-2 agonist (Comparison 03). A variety of beta-2 agonists, oral and inhaled, beta-2 specific and non-specific were used as the comparator in individual studies. No data for symptom-free days could be pooled. Symptom scores and rescue beta-2 agonist use did not differ significantly between xanthine and beta-2 agonists, although hospitalisations were less frequent in participants treated with short-acting beta-2 agonist (NNTH 7). Headache was more frequent with xanthine (NNTH 5), but tremor was less frequent with xanthine (NNTB 4).

Six studies compared xanthine with sodium cromoglycate (Comparison 04). There was no significant difference in symptom free days, symptom scores, rescue beta-2 agonist use or exacerbations. There were fewer gastrointestinal side effects in children given sodium cromoglycate (NNTH 6).

Only one study compared xanthine with ketotifen, and did not report statistical assessment of outcomes.

For xanthines as add-on preventer to inhaled steroids, we identified two comparisons for which we found studies: placebo (comparison 06; three studies) and LTRAs (comparison 07; one study). Due to divergent outcome measures or lack of sufficient numbers of studies, no data from these comparisons were suitable for meta-analysis. The two studies which included more severe, oral steroid dependent patients showed some clinical benefit from adding in xanthine compared with placebo, while the study with milder patients did not. The findings of the study comparing xanthine and LTRA were inconclusive, with statistical testing being reported for change from baseline scores, whilst numerical data were presented for end of treatment values (Kondo 2006).

Assessing the external validity of the assembled evidence is limited by two key aspects of the trials and their presentation. Firstly, ascertaining baseline severity of asthma was hampered by infrequent reporting of baseline lung function assessment. Many of these studies were conducted before inhaled steroids were commonly recommended, and so using pre-trial inhaled steroid consumption as a proxy for severity was not reliable. Based on the available characteristics in the studies, such as symptom frequency, requirement for preventer/reliever medication and the trialists own designation of asthma severity, the majority of children in the included studies had mild to moderately severe asthma.

Secondly, in 17 of the studies there was a pre-study phase in which xanthine was administered to children in an open label fashion, in order to measure blood levels and establish an individualised therapeutic dose. This strategy has the advantages of ensuring that a therapeutic blood level is achieved, while maintaining blinding during the study proper (otherwise measurement of blood levels and dose adjustment would un-blind those in the active limb). However, there are two theoretical disadvantages. Firstly, if children experience mild side-effects which they then recognise later during the study proper, this could itself threaten blinding. Secondly, and perhaps more importantly, it may alter the characteristics of the study population (because children who tolerate xanthines poorly may drop out at this pre-study phase), making the study results more difficult to generalise to asthmatic children as a whole. Hambleton 1977; Nolan 1982 and Pollard 1997 reported attrition rates of 16, 27 and 11% respectively following pre-trial drug exposure phases. Other studies reviewed did not report the drop-out rate during the pre-study phase. It is important for any future studies to document the drop-out rate during any pre-study dose assessment phase and the reasons for this, in order for the importance of this effect to be assessed. Once entered in crossover studies participants who do not complete are unlikely to contribute efficacy data if they do not register any values for the second treatment arm. Where the treatment in question is associated with side-effects, the exclusion of the data for these participants may restrict the generalisability of the treatment populations further, and underestimate the likelihood of side-effects occurring on treatment.

Nevertheless, with these caveats, our analysis suggests that xanthines are of benefit in the treatment of chronic mild to moderate asthma symptoms in children treated for at least four weeks, provided an effective dose of the drug can be achieved without intolerable side effects. The improvements in lung function are large enough to be clinically relevant. These effects are recorded in studies in which the xanthine was the only prophylactic agent used. In the last 30 years, a number of alternative prophylactic agents have been introduced and shown to confer benefit as front line or additive therapy, including inhaled steroids (Adams 2005), long-acting beta-2 agonists (Ni Chroinin 2005; Walters 2007), and leukotriene receptor antagonists (Ducharme 2004). Where economic factors limit the access to these newer agents, our findings suggest that xanthines remain a useful and cost-effective option as sole prophylactic agent. Where newer agents are available, the place of xanthines is less clear. Comparison 02 suggests that xanthines are less effective than inhaled corticosteroids, and supports current guidelines which recommend ICS as the first choice prophylactic agent in symptomatic asthma (BTS 2003).

In steroid-treated asthma where xanthines have been assessed as an additional therapy to corticosteroid treatment, the evidence base is lacking and the few studies that have been conducted to date have reported discrepant effects. The reasons for this may extend beyond purely methodological issues (i.e. sample size, design and duration of studies), but could also encompass baseline severity of the participants and the potency of concomitant steroid therapy given in the studies. Two studies in adults have suggested that adding theophylline to ICS produces similar benefit

to doubling ICS (Evans 1997). Without pooled estimates for this population of children with asthma, exploration of clinical characteristics remains a narrative exercise and as such reinforces the need for further research in this area.

AUTHORS' CONCLUSIONS

Implications for practice

In children who are able to tolerate the potential side-effects of this class of drugs, xanthines given at a therapeutically active dose confer benefit in terms of alleviating symptoms and reducing the requirement for rescue medication in mild and moderate paediatric asthma. However, this review also endorses the view currently held by clinical guidelines that ICS are a more effective first line therapy, as we have found evidence to indicate that ICS lead to fewer exacerbations compared with xanthines. We were unable to find hard evidence to endorse the widely held view that xanthines have an adverse effect on behaviour in children. However, we do not exclude this possible side-effect and we recommend that children who are given the drug be monitored carefully for adverse effects.

In more severe, steroid-dependent asthma the effects of xanthines as an additional therapy (to inhaled and/or oral steroids) have been explored in only a handful of small studies. A narrative synthesis of the trials in this area reveals equivocal effects and further studies would help to establish whether some of the clinically relevant effects reported in the studies are repeatable and consistent. In some parts of the world, xanthines may be more readily available than other therapies, and whilst we do not recommend xanthines above such therapies as inhaled steroids, they may provide a treatment option that will help improve asthma control in their absence.

Implications for research

Future studies should aim to clarify the role of xanthines in the context of first-line preventer treatment, with comparison against inhaled steroids in order to assess the relative effects of xanthines and steroids on symptoms. Several small trials have been performed which compare xanthines with other agents in addition to inhaled steroids. Further work which makes similar comparisons would benefit our understanding of the role of xanthines in second line treatment of asthma in children.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Blumenthal 1980

Methods	Randomised single centre, 3 way crossover study. Withdrawals described. Jadad score: 4
Participants	Numbers enrolled into trial: 29 Numbers in treatment/control treatment periods: 16 (13 withdrawals) Numbers completing trial: 16. Age (range): 5-13 years Age (mean): 8.2 years M/F: 12/4 Asthma severity: Not reported Inclusion criteria: Asthma needing regular daily administration of prophylactic therapy
Interventions	1. Xanth (Phyllocontin) twice daily (adjusted range: 200-550 mg) + salbutamol placebo tablets (three times per day) 2. Placebo xanthine tablets twice daily + salbutamol 0.2 mg/kg/dose (three times per day)

Blumenthal 1980 *(Continued)*

	3. Combination: Xanth and salbutamol at half dose. Study duration: 3 x 5 week treatment periods
Outcomes	FEV1; MMEF; am PEF; pm PEF; symptoms; rescue medication usage
Notes	All patients taking Xanth in pre-trial period adjusted to maintain theophylline level within therapeutic range

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Latin square design
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Double-dummy
Incomplete outcome data addressed? All outcomes	High risk	Crossover study, with data from participants who completed both arms of treatment
Free of other bias?	High risk	All participants exposed to xanthine in a pre-trial dose adjustment phase.

Bose 1987

Methods	Randomised, double-blind, crossover study. Withdrawals reported (no ITT). Jadad score: 4 Statistical analysis: paired t test
Participants	Numbers enrolled into trial: 20 Numbers in treatment/control treatment periods: 20 Numbers completing trial: 17 Age (range): 5-16 years Age (mean): 10.23 (SD 2.70) Asthma severity: Not reported Inclusion criteria: School children attending respiratory clinic over 10 month period; history of recurrent wheeze (6+ episodes lasting more than 24hrs per year) of at least 2 years' duration, despite regular prophylactic Rx with SCG/ß2 BD/inhaled BDP, still had morning/nocturnal cough/wheeze for which they received/being assessed for additional xanthine therapy; Am DIP index >15%; persistent nocturnal cough (7 night per month) Exclusion criteria: Not reported
Interventions	1. Xanth (theophylline 18mg/kg/day) 2. Placebo Study duration: 2 x 4 week treatment period (1 week washout)
Outcomes	Symptoms; PEF; am DIP index; rescue medication usage; serum theophylline level; Side effects
Notes	Participants assessed every 2 weeks during pre-trial period

Bose 1987 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Low risk	Allocation undertaken off-site
Blinding? All outcomes	Unclear risk	Reported as double-blind
Incomplete outcome data addressed? All outcomes	High risk	Crossover study, with data from participants who completed both arms of treatment
Free of other bias?	High risk	All participants exposed to xanthine in a pre-trial dose adjustment phase.

Brenner 1988

Methods	Randomised, double-blind, crossover study. Method of randomisation: Not reported. Screening population/withdrawals not reported. Jadad score: 3 Statistical analysis: Student's t test.
Participants	Numbers enrolled into trial: Not reported Numbers in treatment/control treatment periods: 5 Numbers completing trial: 5 Age (range): 12-15 years Age (mean): Not reported M/F: 1/4 Asthma severity: 'severe' - Systemic steroid dose 10-30mg on alternate days; all taking inhaled BDP: 400-800mcg; all taking regular inhaled treatments of metaproterenol, atropine sulphate and SCG Inclusion criteria: Need for alternate-day CS in spite of additional medication; stability for 4 weeks on lowest dose prednisone/methylprednisone demonstrated to control wheeze; serum levels of xanthine 10mcg/ml-20mcg/ml during 24hr period whilst on xanthine; all taking neb 0.3ml metaproterenol with atropine sulphate 2.0-2.5mg qid; all taking 20mg SCG in nebuliser solution qid; exacerbation free for 4 weeks with baseline FEV1 >/= 80% predicted at beginning of each treatment period
Interventions	1. Xanthine (serum theophylline levels to be kept between 12mcg/ml and 16mcg/ml + usual therapy (including ICS, SCG, ß-agonists, OCS) 2. Placebo + usual therapy Study duration: 4 week treatment period in 3 participants, 3 week Rx in 2 participants (due to worsening symptoms on placebo No washout period described
Outcomes	Symptoms; FEV1; exacerbations; additional medication
Notes	Patients initially recruited from in-patient setting. Dose of theophylline kept within therapeutic range

Risk of bias

Brenner 1988 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Unclear risk	Described as double-blind
Incomplete outcome data addressed? All outcomes	High risk	Crossover study, with data from participants who completed both arms of treatment
Free of other bias?	High risk	All participants exposed to xanthine in a pre-trial dose adjustment phase.

Carswell 1983

Methods	Randomised, double-blind, crossover study. Method of randomisation: Not reported. Screening population/withdrawals not reported. Withdrawals: 5 participants withdrew prior to randomisation. All remaining 18 completed study. Jadad score: 3 Statistical analysis: paired t test
Participants	Numbers enrolled into trial: 23 Numbers in treatment/control treatment periods: 18 Numbers completing trial: 18 Age (range): 1.5-6 years Age (median): 3.7 years M/F: 12/6 Asthma severity: 'severe' - all required prophylactic therapy . All 18 participants completing the study had a positive skin prick test. Inclusion criteria: As above. no other entry criteria were reported ation free for 4 weeks with baseline FEV1 >/= 80% predicted at beginning of each treatment period
Interventions	1. Xanthine (12mg/kg/BID - adjusted where necessary to give serum levels of 56 to 112 mmols/L) 2. Ketotifen 0.25 to 0.5mg BID 3. Placebo Study duration: 3x6 week treatment periods. Data presented only for last four weeks of treatment to avoid carryover.
Outcomes	% days of symptom score low (1/0); % days no salbutamol given; % days no additional prednisolone given; % days hospital admission necessary
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Unclear risk	Information not available

Carswell 1983 *(Continued)*

Blinding? All outcomes	Unclear risk	Described as double-blind
Incomplete outcome data addressed? All outcomes	High risk	Crossover study; data from participants who completed all arms of treatment
Free of other bias?	Low risk	No pre-trial xanthine exposure phase performed

Chow 1989

Methods	Randomised, double-blind, double dummy crossover study. Method of randomisation: Latin square design (block randomisation). Withdrawals: None. Jadad score: 5 Statistical analysis: ANOVA
Participants	Numbers enrolled into trial: 24 Numbers in treatment/control treatment periods: 24 Numbers completing trial: 24 Age (range): 7-17 Age (mean): M/F: 17/7 Asthma severity: Moderate-severe. Perenial asthma defined by ATS; Mean FEV1 (L): 1.3 (SD 1.36), 74.4% predicted; PEF (L/min): 235 (SD 64), 78.8% predicted Pre-trial dose of Xanthine 200mcg daily (bid) for 7 days Inclusion criteria: FEV1 and PEF between 40-80% predicted; one of these outcomes had to increase by at least 20% after 50mcg terbutaline inhalation; serum theophylline level between 8-20mg/L post pre-trial dosing protocol; spontaneous PEF diurnal variation <30% included in the study Exclusion criteria: Current smokers; renal/hepatic/cardiovascular/thyroid disease; respiratory tract infections; pneumonia; recent exacerbation of asthma/medication change; use of CS, SCG, anticholinergics, ketotifen, calcium channel blockers prior to study
Interventions	1. Sustained release terbutaline (5mg BID) + xanthine (theophylline) placebo 2. Sustained release xanthine (theophylline 200mg BID) + terbutaline placebo 3. Terbutaline (5mg BID) + xanthine (theophylline 200mg BID) 4. Terbutaline placebo + xanthine placebo Study duration: 4x4 week treatment periods. Data aggregated for day 6-28 to avoid carryover effect in first 5 days.
Outcomes	Symptoms; PEF; FEV1; FVC; rescue medication usage; preference; side effects
Notes	Source of participants: hospital OPD Participants were permitted to use inhaled ß2 agonist prn, other anti-asthma drugs were prohibited.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available

Chow 1989 *(Continued)*

Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Double-dummy design
Incomplete outcome data addressed? All outcomes	High risk	Crossover study; data from participants who completed all arms of treatment
Free of other bias?	Low risk	No pre-trial xanthine exposure phase performed

Conway 1986

Methods	Randomised, double-blind crossover study. Withdrawals: 13. (Non ITT). Jadad score: 3 Statistical test: Paired t test and Wilcoxon for non-parametric data.
Participants	Numbers enrolled into trial: 29 Numbers in treatment/control treatment periods: 29 Numbers completing trial: 16 Age (range): 10 months to 4 years Age (mean): 2.6 years M/F: Not reported Asthma severity: Moderate 14/16 family history atopic asthma; 9 with eczema; mean age onset of symptoms 1.1 years; frequency symptoms range: several times weekly to <once weekly; 10/16 previous hospital admission with asthma Inclusion criteria: Children </=4 years of age; diagnosed asthma; OPD referral/referral after acute admission; history recurrent wheeze/cough; resolving spontaneously/with treatment.
Interventions	1. Xanthine (slophyllin mean dose 10.3 mg/kg/dose 2. Placebo Concomitant ICS at discretion of treating physician. ß-agonist prn. Study duration: 4 x 6 weeks alternating treatment (i.e. AB BA AB BA versus BA AB BA AB).
Outcomes	Symptoms; adverse events; additional medication; hospital admissions; parental preference
Notes	No washout phase described -data from week 1 of each treatment phase discarded.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Unclear risk	Described as double-blind
Incomplete outcome data addressed? All outcomes	High risk	Crossover study; data from participants who completed all arms of treatment. Data presented from last 5 weeks of treatment to avoid carryover.

Conway 1986 *(Continued)*

Free of other bias?	Low risk	No pre-trial xanthine exposure phase performed

Dusdieker 1982

Methods	Randomised, double-blind, double dummy, crossover study. Withdrawals: 5 (non-ITT). Jadad score: 3 Statistical test: paired t test
Participants	Numbers enrolled into trial: 38 Numbers in treatment/control treatment periods: 38 Numbers completing trial: 33 Age (range): 6 to 16 years Age (mean): 12 years M/F: 20/18 Asthma severity: Mild/moderate Age at onset: 1-12 years (mean 4 years); inhaled metaproterenol or terbutaline had been used by most participants for occasional symptoms/short course prednisone when symptoms unresponsive to BD; None had required short course of OCS/ICS in previous month. Inclusion criteria: All adequately controlled with theophylline as only continuous medication; reversibility with BD/CS previously documented Exclusion criteria: Continuous rx with CCG/OCS/ICS
Interventions	1. Xanthine (theophylline) 3 times/day + dummy oral ß-agonists 2. Placebo xanthine + oral ß2-agonists Study preceded by 14 day run-in whereby xanthine administered to ensure that peak serum concentration between 10-20mcg/ml. Study duration: 2 x 4 week treatment periods. No washout phase reported.
Outcomes	Sypmtoms; PEF; rescue medication usage; OCS usage; preference; adverse effects
Notes	Participants excluded if exacerbations not resolved with OCS treatment within 24hours for more than 7 days/month

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Low risk	Randomisation code known by pharmacist
Blinding? All outcomes	Low risk	Double-dummy
Incomplete outcome data addressed? All outcomes	High risk	Crossover study; data from participants who completed all arms of treatment. Data presented from last 5 weeks of treatment to avoid carryover.
Free of other bias?	High risk	All participants exposed to xanthine in a pre-trial dose adjustment phase.

Edmunds 1980

Methods	Randomised crossover study. Withdrawals: not reported. Jadad score 2 Staistical analysis: unclear
Participants	Numbers enrolled into trial: not reported Numbers in treatment/control treatment periods: 30 Numbers completing trial: 30 Age (range): 5-15 Age (mean): Not reported M/F: 17/13 Asthma severity: Not fully described Inclusion criteria: Children aged 5-15 with 'perennial asthma'
Interventions	1. Xanthine (slow release aminophylline - 10-20mcg/ml) BID + placebo inhaler QID daily 2. Placebo Xanth BID + inhaled SCG QID 3. Placebo Xanth BID + placebo inhaled SCG QID Study duration: 3 x 4 week treatment periods. No washout phase described.
Outcomes	Symptoms/symptom free days; PEF; rescue medication usage (salbutamol); compliance
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Double-dummy
Incomplete outcome data addressed? All outcomes	Unclear risk	Not enough information available to determine how many participants withdrew from randomisation
Free of other bias?	High risk	All participants exposed to xanthine in a pre-trial dose adjustment phase.

Evans 1981

Methods	Randomised, crossover study. Withdrawals: 3. Jadad score: 3 Statistical analysis: Mann-Whitney tests
Participants	Numbers enrolled into trial: 25 Numbers in treatment/control treatment periods: 25 Numbers completing trial: 22 Age (range): 5.2 to 15.3 years Age (mean): 9.3 M/F: Not reported Asthma severity: Unclear - diagnosis and profile patients described in terms of nocturnal symptoms Inclusion criteria: Nocturnal symptoms 'a major clinical problem'

Evans 1981 *(Continued)*

Interventions	1. Xanthine (slow release aminophylline) once daily (bedtime) 2. Placebo Study duration: 2 x 4 week treatment periods. No washout phase described.
Outcomes	PEF (am and pm); relief medication; symptoms PEF disregarded if other relief medication used within 6 hours
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Unclear risk	Described as double-blind
Incomplete outcome data addressed? All outcomes	Low risk	All participants completed the study
Free of other bias?	Low risk	No pre-trial xanthine exposure phase

Furukawa 1984

Methods	Randomised parallel group trial. Withdrawals: Xanth/SCG: 5/1 (no ITT). Jadad score: 4
Participants	Numbers enrolled into trial: 46 Numbers in treatment/control treatment groups: Xanth/SCG: 18/22 Numbers completing trial: 18/22 Age (range): 5-15 years Age (mean): Xanth/SCG: 8.8/8.1 years M/F: Xanth: 11/7; SCG: 17/5 Asthma severity: Moderate-severe FEV1 (Xanth/SCG): 75.06/78.14% predicted; FVC (Xanth/SCG): 82.56/85.23 % predicted; FEF25-75 (Xanth/SCG): 60.78/56.36; PEF: (Xanth/SCG): 86.44/85.33 Inclusion criteria: Diagnosis of asthma confirmed by +ve results for methacholine test - decrease in FEV1 >20% at methacholine challenge level of <100 breath units (provocative dose of </= 10ng/mL concentration methacholine); daily symptoms of coughing/chest congestion/wheeze; not receiving medication
Interventions	1. Xanthine (theophylline) BID + placebo inhaled SCG QID 2. Placebo xanthine BID + inhaled SCG QID Dosage of Xanth given as 200-600mg and increased so as to minimise side effects in week 1. Therapeutic threshold attained was 10-15mcg/mL. SCG dosage 80mg/d initially - down titrated Study duration: 12 weeks

Furukawa 1984 *(Continued)*

Outcomes	Improvement in asthma severity; participants with reduction bronchial reactivity; study withdrawal; side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	'Randomly generated code'
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Double-dummy
Incomplete outcome data addressed? All outcomes	High risk	Data from participants who completed the study were used in the analysis
Free of other bias?	Low risk	No pre-trial xanthine exposure phase

Galant 1996

Methods	Randomised parallel group trial. Withdrawals: 140. Jadad score: 4
Participants	Numbers enrolled into trial: 353 Numbers in treatment/control treatment groups: Xanth: 89; FP50: 91; FP100: 86; PLA: 87 Numbers completing trial: Xanth: 48; FP50: 70; FP100: 63; PLA: 38 Age (range): 12-75 Age (mean): Xanth: 29; FP50: 30; FP100: 29; PLA: 30 M/F (%): Xanth: 63/37; FP50: 68/32; FP100: 69/31; PLA: 67/33 Asthma severity: mild-moderate Inclusion criteria: stable reversible asthma; >/= 12 years; requirement for daily rx of asthma; serum theophylline level trough concn <3.5mg/L; FEV1 45-75% predicted; >/-15% increase FEV1 15 mins post SABA; compliant during run-in phase. Exclusion criteria: Pregnancy; history life-threatening asthma; hypersensitivity to sympathomimetic drugs/CS; smoking in previous year; history of >10 pack years; use of OCS/injectable steroids in previous 12 weeks; alternate day CS for >2 months in previous 2 years Baseline data: FEV1 (L) (mean (SEM)): Xanth: 2.40 (0.05); FP50: 2.44 (0.05); FP100: 2.29 (0.06); PLA: 2.31 (0.06); % predicted: Xanth: 62; FP50: 62; FP100: 60; PLA: 61
Interventions	1. Xanthine (theophylline 100 mcg; two capsules BID) + placebo FP inhaler (two puffs BID) 2. Placebo xanthine (two capsules BID) + FP50 (two puffs BID; total dose 200mcg) 3. Placebo xanthine (two capsules BID) + FP100 (two puffs BID; total dose 400mcg) Study duration: 12 weeks
Outcomes	Symptoms; am pre dose FEV1; am and pm PEF; rescue medication use; no night awakenings; global assessment (physician rating)
Notes	Included as participants under 18 were recruited. No data for pooled population are entered.

Galant 1996 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Double-dummy
Incomplete outcome data addressed? All outcomes	High risk	Efficacy population defined as: '...patients with no major protocol violations who remained in the study, i.e. those meeting protocol-defined continuation criteria up to and including their last study visit (defined as endpoint)...'
Free of other bias?	Low risk	No pre-trial xanthine exposure phase

Gil 1993

Methods	Randomised, crossover trial. Withdrawals: None reported. Jadad score: 3 Statistical test: Friedman's and Dunn's tests with level of significance $P < 0.05$
Participants	Numbers enrolled into trial: not reported Numbers in treatment/control treatment groups: 21 Numbers completing trial: 21 Age (range): 7.5 years - 13.15 years Age (mean): Not reported M/F (%): Not reported Asthma severity: mild-moderate Inclusion criteria: Mild or moderate asthma, no BD for 30 days, IQ between 80-101. Exclusion criteria: Neurological/psychiatric disorders Baseline data: FEV1 (L) (mean): 2.48 Inclusion criteria: asthma Exclusion criteria: BD in last 30 days
Interventions	1. Xanthine (theophylline 600mcg/d; mean xanthine dose: 12.1 mcg/ml) 2. Placebo Study duration: 4 weeks. No washout period described.
Outcomes	Psychological evaluation (Wechsler Belleuve Scale)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available

Gil 1993 *(Continued)*

Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Unclear risk	Described as double-blind
Incomplete outcome data addressed? All outcomes	Unclear risk	Not enough information available to determine how many participants withdrew from randomisation
Free of other bias?	Low risk	No pre-trial xanthine exposure phase

Glass 1981

Methods	Randomised crossover trial. Withdrawals: not described. Jadad score: 2 Statistical analysis: The Mantel-Haenszel test was applied to the data with pair wise comparison of placebo and drugs for each of the 4 main symptoms
Participants	Numbers enrolled into trial: not reported Numbers in treatment/control treatment periods: 16 Nummbers completing trial: 16 Age (range): 1.75 years to 4.5 years Age (mean): 3.5 years M/F: 11/5 Asthma severity: Not reported. 15/16 personal/family history of atopy; wheeze precipitated by URTI in 15/16, by exercise in 11/16, by specific allergens in 5/16; 7/11 children had +ve skin tests. Median 2 hospital admissions per child in previous year. 15/16 children had received CS treatment (0 on maintenance Rx); 7/16 intermittent/regular SABA Rx; 6/16 SABA + Xanth; 2/16 Xanth alone; 1/16 regular orciprenaline alone Inclusion criteria: <5 years old; poor control of asthma with routine Rx; at least 2 wheezing episodes during 6 weeks pre-trial
Interventions	1. Xanthine (oral theophylline 6-8 mg/kg, mean 6.7; QID) 2. nebulised SCG (20mg diluted in 2ml sterile water) 3. Placebo (unclear whether this was oral/nebulised) Study duration: 3 x 8 week treatment periods.
Outcomes	Symptoms; rescue medication usage; intercurrent illness; short-term course of CS; admission to hospital; parental preference.
Notes	No titration of theophylline dose. 50% were in therapeutic range. Concealment of allocation established through telephone contact with trialist

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Low risk	Randomisation off-site by third party not involved with the study
Blinding?	Unclear risk	No explicit description of masking of treatments

Glass 1981 *(Continued)*

All outcomes		
Incomplete outcome data addressed? All outcomes	Unclear risk	Not enough information available to determine how many participants withdrew from randomisation. Data from first 2 weeks of each treatment phase were disregarded
Free of other bias?	Low risk	No pre-trial xanthine exposure phase

Hambleton 1977

Methods	Randomised crossover study. Withdrawals: 0 (10 Patients withdrawn after pretrial exposure to Xanth). Jadad score: 4. Statistical analysis: Two way analysis of variance with Tukey's modification to allow for paired comparisons. IPD published for symptom free days, PEF and no. emergency treatments.
Participants	Numbers enrolled into trial: 28 Numbers in treatment/control treatment periods: 28 Numbers completing trial: 28 Age (range): 6-15 years Age (mean): 10.6 years M/F: 24/4 Asthma severity: Not reported Medication at baseline: SCG + SABA: 13; Xanth + SABA: 11; Xanth, SCG + SABA: 4. No lung function/symptom scores reported. Inclusion criteria: Asthma needing daily medication; tolerance of Xanth; Exclusion criteria: Requirement of OCS within 4 weeks.
Interventions	1. Xanthine (individually adjusted theophylline, mean 6.0 mcg/kg, QID) + placebo SCG inhaler (QID) 2. Placebo Xanth (QID) + SCG (20mcg QID) versus Xanth (QID) + SCG (QID) Concomitant medication: SABA; OCS if symptoms inadequately controlled Study duration: 3 x 4 week treatment periods. No washout period described.
Outcomes	Symptoms; am/pm PEF; rescue medication usage; treatment failure; adverse effects
Notes	Patients excluded who could not tolerate Xanthine in run-in phase.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Latin square design
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Double-dummy
Incomplete outcome data addressed? All outcomes	Low risk	All participants completed the study

Hambleton 1977 *(Continued)*

Free of other bias?	High risk	All participants exposed to xanthine in a pre-trial dose adjustment phase.

Joad 1986

Methods	Randomised, double-blind crossover study. Method of randomisation: not reported. Concealment of allocation: unclear. Withdrawals: 0. Jadad score: 3.
Participants	Numbers enrolled into trial: not reported Numbers in treatment/control treatment periods: 18 Numbers completing trial: 18 Age (range): 13-70 years Age (median): 29 years M/F: not reported Asthma severity: Not reported. All patients had ATS defined asthma. Previous therapy included maintenance Xanth and inhaled SABA prn. 8/18 participants receiving ICS (BDP, median dose 600mcg/day), 1/18 receiving OCS (30mcg prednisone on alternate days). All participants met previously defined criteria for control of asthma (according to clinic protocol) Inclusion criteria: ATS defined asthma; extended history of symptoms >50% days in absence of medications; at least 1+ve skin prick test Exclusion criteria: SCG in 4 weeks prior to study
Interventions	1. Xanthine (slow release theophylline, 10-20mcg/mL BID) + placebo SABA inhaler QID 2. Placebo xanthine (QID) + SABA (albuterol 200mcg, QID) 3. Xanthine + SABA Study duration: 3 x 4 week treatment periods.
Outcomes	Symptoms (diary); compliance; side-effects; preference; PEF; rescue medication usage
Notes	Included as participants under 18 were recruited. No data for pooled population are entered. Participants correctly identified the treatment they received in 38% study periods Participants maintained prior CS treatment

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Double-dummy
Incomplete outcome data addressed? All outcomes	Unclear risk	Not enough information available to determine how many participants withdrew from randomisation. Diary derived data not used from first 6 days of treatment periods.
Free of other bias?	Low risk	No pre-trial xanthine exposure phase

Kondo 2006

Methods	Randomised, open label, parallel group study. Method of randomisation: Minimisation. Withdrawals described (LOCF). Jadad score: 3
Participants	Numbers enrolled into trial: 84 Numbers in treatment/control treatment periods: 75 Numbers completing trial: 79 Age (range): 6-14 years Age (mean): 9 years M/F: 44/31 Asthma severity: Mild to moderate (GINA) ICS dose: 248mcg/d (BDP equivalent) Inclusion criteria: Reversible PEF; symptoms during 2 week run-in; low dose ICS Exclusion criteria: use of systemic or parernteral corticosteroids; use of oral antiallergic drugs 2 weeks prior to run-in; patients who used a LABA within the 1 year prior to run-in; complications that could affect the evaluation of efficacy, such as bronchiectasis; history of serious adverse drug reaction to theophylline or other xanthine derivatives; previous use of montelukast
Interventions	1. Xanthine (sustained release theophylline 5-8mg/kg dry syrup, or 100-200mg tablet) twice daily + ICS 2. Montelukast 5 mg chewable tablet administered once daily at bedtime + ICS All participants given stable dose ICS during run-in Study duration: 4 weeks
Outcomes	Morning & evening PEF; symptoms; rescue medication use; exacerbations of asthma; adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	'...allocation of the study drug was performed using the minimization method involving study centers and body weight as factors.'
Allocation concealment?	Low risk	Centralised randomisation process.
Blinding? All outcomes	High risk	Open label design
Incomplete outcome data addressed? All outcomes	High risk	Last observation carried forward
Free of other bias?	Low risk	No pre-trial xanthine exposure phase

Levene 1986

Methods	Randomised crossover study. Withdrawals: 9. Non-ITT. Jadad score: 4

Levene 1986 *(Continued)*

	Statistical test: Paired t test.
Participants	Numbers enrolled into trial: 24 Numbers in treatment/control treatment periods: 15 Numbers completing trial: 15 Age (range): 5 years-12 years 11 months Age (mean): Not reported M/F: Not reported Asthma severity: moderate Inclusion criteria: Requirement for regular prophylaxis (not steroids); able to use peak flow meter; able to swallow tablets; parents able to read peak flow meter scales and complete diary cards. Exclusion criteria: Requirement for O/ICS; more than 3 wheezy episodes in three months;
Interventions	1. Xanthine (sustained release theophylline, approximately 20mg/kg to nearest 100mg, OD) 2. Placebo Study duration: 2 x 6 week treatment periods.
Outcomes	Symptoms; am and pm PEF; rescue medication usage; adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Unclear risk	Information not provided
Blinding? All outcomes	Low risk	'...identical placebo'
Incomplete outcome data addressed? All outcomes	High risk	Crossover study; data analysed from participants who completed all arms of treatment. Data from last 28 days only analysed.
Free of other bias?	High risk	All participants exposed to xanthine in a pre-trial dose adjustment phase.

MacDonald 1979

Methods	Randomised, double-blind crossover study. blinding: not reported; Withdrawals: 2. ITT; Jadad score: 2 Statistical test: paired t test
Participants	Numbers enrolled into trial: 10 Numbers in treatment/control treatment periods: 8 (2 withdrawals) Numbers completing trial: 8 Age (range): 8-12 years M/F: 5/5 Asthma severity: Not reported Inclusion criteria: Diagnosis of allergic asthma (+ve skin prick test; nasal provocation; specific IgE), asymptomatic at time of entry

MacDonald 1979 *(Continued)*

Interventions	1. Xanthine (slow release aminophylline - phyllocontion continus, 12.5mg/kg BID) 2. Placebo Study duration: 2 x 4 week treatment periods. Participants given SCG 20mg QID for 4 weeks prior to study entry
Outcomes	Symptoms; additional medication usage; am and pm PEF
Notes	No washout phase described

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	Date of birth used as a means of generating allocation sequence
Allocation concealment?	High risk	Date of birth known by both participants and investigators
Blinding? All outcomes	Unclear risk	Described as double-blind
Incomplete outcome data addressed? All outcomes	High risk	Crossover study; data analysed from participants who completed all arms of treatment. Data from last 2 weeks contributed to the analysis.
Free of other bias?	High risk	All participants exposed to xanthine in a pre-trial dose adjustment phase.

Meltzer 1992

Methods	Randomised, double-blind, parallel group trial. withdrawals: xanthine+SABA: 13; BDP+SABA: 4; xanthine+BDP+SABA: 6. Jadad score: 4
Participants	Numbers enrolled into trial: 111 Numbers in treatment/control treatment periods: 104 Numbers completing trial: 88 Age (range): 6-16 years Age (mean): 8.2 years M/F: 34/77 Asthma severity: Moderate Participants had chronic asthma with significant BD response. FEV1 % pred (+/- SEM): Xanth+SABA: 67 (2.5); SABA+BDP: 71 (3.0); Xanth+SABA+BDP: 70 (3.4); FVC % pred: Xanth+SABA: 83 (3.2); SABA+BDP: 82 (2.4); Xanth+SABA+BDP: 86 (3.4); FEF25-75 % pred: Xanth+SABA: 63 (6.4); Xanth+BDP: 68 (7.2); Xanth +SABA+BDP: 62 (6.5) Inclusion criteria: Age 6-16 years with chronic asthma; unstable despite daily medication; use of beta-agonists; FEV1</=75%; FEV1 reversibility >/= 15% post-BD Exclusion: Requirement of regular OCS
Interventions	1. Xanthine (oral theophylline - titrated to achieve serum levels of 8/18mcg/ml) BID + SABA 2. BDP (42mcg) via MDI 2 puffs QID + SABA 3. Xanthine (oral theophylline) BID + BDP (42mcg) via MDI 2 puffs QID + SABA Study duration: 12 weeks

Meltzer 1992 *(Continued)*

Outcomes	Lung function; serum theophylline levels; symptoms; sleep quality; adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Indistinguishable dummy capsules
Incomplete outcome data addressed? All outcomes	Unclear risk	Not enough information available on definition of population analysed
Free of other bias?	Low risk	No pre-trial xanthine exposure phase

Nassif 1981

Methods	Design: randomised, double-blind, crossover study. Method of randomisation: unclear. Blinding: double-blind, identical placebo. Description of withdrawals or dropouts: yes (all participants completed). Jadad's score: 4. Statistical analysis: paired t test.
Participants	Numbers enrolled into trial: 33 Numbers in treatment/control treatment periods: 33 Numbers completing trial: 33 Age (range): 7-19 Age (mean): ICS pts: 13.6 (N = 22); alternate day prednisone 11.8 (N = 11) Age at onset of asthma: 3.1/2 M/F: Not reported Asthma severity: steroid dependent Inclusion criteria: Children with chronic asthma; steroid-dependent (lowest steroid dose compatible with disease control); all continuous medication stable during prior 3 months. Exclusion criteria: Exacerbations requiring additional daily CS in previous month
Interventions	1. Xanthine (slow release theophylline, Theo-Dur, bid or tid depending on needs of individual patient) + ICS or OCS 2. Placebo xanthine + ICS or OCS Serum theophylline concentration: 8 to 24 microgram/ml achieved, mean 15.5 microgram/ml. Duration: 2 x 4 weeks. Data recorded over last two weeks of study period.
Outcomes	Symptoms; PEF; need to terminate treatment period; pulmonary function tests; exercise stress test; preference; adverse events Additional notes: data from first 2 days of each study period were eliminated. All data collected while patients were on additional doses of prednisone were eliminated from analysis.

Nassif 1981 *(Continued)*

Notes	Data for ICS participants used as OCS not considered by this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Low risk	Information not available
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed? All outcomes	Low risk	All participants completed the study
Free of other bias?	High risk	All participants exposed to xanthine in a pre-trial dose adjustment phase.

Newth 1982

Methods	Randomised crossover study. Description of withdrawals or dropouts: yes. ITT - assumed not. Jadad score: 4. Statistical analysis: Friedman two way analysis of variance. Data on % symptom free days, % days when salbutamol required and theophylline levels were given as IPD.
Participants	Numbers enrolled into trial: 28. Numbers in treatment and control groups: 28 in each group (crossover design). Numbers of withdrawals or dropouts: 2. Numbers completing trial: 26. Age (range): 13 months to 5 years at entry, of those completing study. Age (mean): 3.1 years. Asthma diagnosis: chronic asthma. Inclusion criteria: age 1 to 6 years, asthma needing regular daily administration of medications, no need for corticosteroids in preceding month.
Interventions	1. Xanthine (theophylline, liquid Somophyllin) every 6 hours). Theophylline dose (mean): start of trial - 6.1mg/kg/dose q6h, end of trial - 5.6mg/kg/dose q6h.Theophylline dose (range): start of trial - 4.3 to 8.1 mg/kg/dose q6h, end of trial - 3.8 to 8.2 mg/kg/dose q6h. Serum theophylline concentration: 10 to 20 mg/l. 2. Nebulised sodium cromoglycate 20mg of 1% Intal qid 3. Xanthine and sodium cromoglycate as above. Duration: total = 24 weeks, 3 x 8 weeks, plus 1 to 4 weeks of pre-study period. First 3 weeks of each treatment phase were not analysed. Additional notes: salbutamol allowed for acute symptoms.
Outcomes	Diary of nocturnal and daytime wheeze and cough, exercise tolerance, appetite.
Notes	

Risk of bias

Newth 1982 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Unclear risk	Information not provided
Blinding? All outcomes	Low risk	Double-dummy; xanthine capsules indistinguishable in colour and taste.
Incomplete outcome data addressed? All outcomes	High risk	Crossover study; data analysed from participants who completed all arms of treatment.
Free of other bias?	High risk	All participants exposed to xanthine in a pre-trial dose adjustment phase.

Nolan 1982

Methods	Design: randomised crossover study. Description of withdrawals or dropouts: Xanth: 1. Jadad's score: 4. Statistical test: ANOVA - matched comparison of patient scores under each treatment. Paired t test were used to compare differences between treatment regimens.
Participants	Numbers enrolled into trial: 22. Numbers in treatment and control groups: 22 in each group (crossover design). Numbers of withdrawals or dropouts: 7 (6 during theophylline run-in phase, 1 during fenoterol phase). Numbers completing trial: 15. An additional 4 were excluded from final analysis. Age (range): 1.6 to 6.6 years, of 15 completing trial. Age (mean): 3.8 years, at entry of trial, of those 15 completing trial. Sex (male/female): 10/5. Asthma diagnosis: episodic dyspnoea, wheeze and cough, rhonchi and hyperinflation on examination. Severity of asthma: moderately severe, non-steroid dependent. Inclusion criteria: < = 6 years old, asthma symptoms at least weekly, on long-term continuous asthma medication, above 10th percentile for height and weight. None were receiving continuous inhaled or oral corticosteroid treatment, and all were receiving previous theophylline preparations. 7 had been taking inhaled or oral sympathomimetics and 3 were on long terms sodium cromoglycate. All had received emergency room treatment in the last year.
Interventions	1. Xanthine: sustained release (SR) theophylline anhydrous capsules (Theobid Jr, 130mg per capsule, bid). Serum theophylline concentration: adjusted for range within 10 to 20 microgram/ml. 2. Controlled release (CR) albuterol tablet (Volmax, 8mg, BID). Duration: 12 weeks. No washout phase described.
Outcomes	Diary of symptoms (nighttime symptoms, daytime cough, wheeze, activity, appetite), additional medication, hospital admissions, infections, compliance. Adverse events (any).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available

Nolan 1982 *(Continued)*

Allocation concealment?	Unclear risk	Information not provided
Blinding? All outcomes	Low risk	Double-dummy
Incomplete outcome data addressed? All outcomes	High risk	Crossover study; data analysed from participants who completed all arms of treatment.
Free of other bias?	High risk	All participants exposed to xanthine in a pre-trial dose adjustment phase.

Pedersen 1983

Methods	Randomised, crossover study. Description of withdrawals or dropouts: all completed. Jadad's score: 4. Statistical analysis: Paired t test
Participants	Numbers enrolled into trial: 19. Numbers in treatment and control groups: 19 in each group (crossover design). Numbers of withdrawals or dropouts: 0. Numbers completing trial: 19. Data from 2 patients were excluded from final analysis. Age (range): 6 to 12 years. Age (mean): 8.7 years. Sex (male/female): 9/10. Asthma diagnosis: severe perennial asthma, type D according to McNicol-Williams classification. Inclusion criteria: inadequate control of asthma, in spite of continuous prophylactic medication with disodium cromoglycate or in combination with terbutaline. Source of participants: outpatient clinic.
Interventions	1. Xanthine: sustained release theophylline (BID). Serum theophylline concentration (range): 7.8 to 19.4 mg/l. Serum theophylline concentration (mean): 13.3 mg/l. 2. Placebo Duration: 6 weeks, 2 x 3 weeks. Initally there was a 2 week pretrial period, followed by one year with theophylline treatment. After this period the participants were randomised into the 6 week trial. Data from first week were not evaluated.
Outcomes	Diary of PEF, bronchoconstriction attacks, additional medication. Adverse events (any). FEV1.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Unclear risk	Information not provided
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed?	Low risk	All participants completed the study

Pedersen 1983 *(Continued)*
All outcomes

Free of other bias?	High risk	All participants exposed to xanthine in a pre-trial dose adjustment phase.

Pierson 1990

Methods	Design: randomised parallel group study. Description of withdrawals or dropouts: yes. Jadad's score: 4.
Participants	Numbers enrolled into trial: 124. Number in treatment group: 62. Number in control group: 62. Numbers of withdrawals or dropouts (treatment group): 0. Numbers of withdrawals or dropouts (control group): 1, due to adverse event. Numbers completing trial (treatment group): 62. Numbers completing trial (control group): 61. Age (range): treatment group - 13 to 56 years, control group - 12 - 67 years. Age (mean +/- SD): treatment group - 29 +/- 11.8 years, control group - 28 +/- 12.6 years. Sex (male/female): treatment group - 37/25, control group - 41/21. Asthma diagnosis: chronic reversible obstructive airway disease, as defined by ATS. Inclusion criteria: > = 12 years old, diagnosed (defined by ATS) as having chronic reversible obstructive airway disease, received theophylline daily > = 30 days before enrolment, pre-treatment FEV1 < = 80% predicted, FEV1 > = 15% or FEF 25-75 > = 25% increase after inhalation of 160 microgram of isoproterenol. Exclusion criteria: pregnant, lactating, emotional or physical problems, taken cromolyn sodium or oral corticosteroids 2 weeks before enrolment, previous adverse reactions to sympathomimetic agents or methylxanthines, any abnormal findings in laboratory or physical examinations. Source of participants: 4 study centres.
Interventions	1. Xanthine: sustained release (SR) theophylline anhydrous capsules (Theobid Jr, 130mg per capsule, bid). Serum theophylline concentration: adjusted for range within 10 to 20 microgram/ml. 2. Controlled release (CR) albuterol tablet (Volmax, 8mg, bid). Duration: 12 weeks.
Outcomes	Diary of PEFR, symptom scores, asthma medication. Pulmonary function tests, pulse rate, blood pressure, ECG. Adverse events (any). Additional notes: participants were given inhaled albuterol sulfate for use on an as-needed basis.
Notes	Included as participants under 18 were recruited. No data for pooled population are entered.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Unclear risk	Double-dummy; matching placebo
Incomplete outcome data addressed? All outcomes	Low risk	Low attrition rate (1 in SABA group)

Pierson 1990 *(Continued)*

Free of other bias?	High risk	All participants exposed to xanthine in a pre-trial dose adjustment phase.

Pollard 1997

Methods	Randomised parallel group study. Withdrawals: Xanth: 27; SAL: 27; PLA: 26. ITT population. Jadad score: 3
Participants	Numbers enrolled into trial: 484 (154 withdrawn pre-randomisation, of which 71 due to xanthine-related SEs) Numbers in treatment/control treatment groups/periods: Xanth: 162; SAL: 162; PLA: 160 Numbers completing trial: Xanth: 135; SAL: 135; PLA: 134 Age (range): 12-75 years Age (mean): Xanth: 30; SAL: 31; PLA: 33.8 M/F: Xanth: 46/54; SAL: 48/52; PLA: 51/49 Asthma severity: Moderate (Asthma defined by ATS criteria) Mean FEV1: Xanth: 2.65 (71% pred); PLA: 2.63 (73% pred); SAL: 2.60 (72% pred); mean am PEF (L/min): Xanth: 434.2; SAL: 424.7; PLA: 425.1; mean pm PEF: Xanth: 451.4; SAL: 447.9; PLA: 447; ICS use: Xanth: 54%; SAL: 54%; PLA: 58%; Xanth use: 37%; SAL: 35%; PLA: 36% Inclusion criteria: >/=12 years; ATS defined asthma requiring daily treatment; FEV1 >50% % predicted; FEV1 reversibility: 15% post-BD. Exlcusion criteria: hypersensitivity to methylxanthine; any medication affecting asthma; other serious disease; respiratory infection in previous 4 weeks; ECG abnormality; use of OCS/parenteral CS in last 4 weeks
Interventions	1. Xanthine (slow release theophylline, serum concentration: 10-20mg/L BID) + placebo SAL 2. Placebo xanthine + SAL: 42mcg (via MDI) BID 3. Placebo xanthine + placebo SAL Study duration: 12 weeks (+ 1-2 week baseline period)
Outcomes	Symptoms; PEF; rescue medication usage; physician rated effectiveness; adverse events
Notes	Included as adults and children were recruited. Data not entered for pooled population estimates. 35-37% participants had previously used Xanth - possible cause of confounding; intolerance to xanthine an exclusion criteria - selection bias?

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Unclear risk	Double-dummy
Incomplete outcome data addressed? All outcomes	Unclear risk	Intention to treat population defined as: 'all patients who received study drug...'
Free of other bias?	High risk	All participants exposed to xanthine in a pre-trial dose adjustment phase.

Rachelefsky 1980

Methods	Randomised crossover study. Withdrawals: all participants completed (no reporting of numbers screened): Jadad score: 2 Statistical analysis: Wilcoxon signed rank sum test based on within patient differences (difference in mean outcome data for 4 week treatment period)
Participants	Numbers enrolled into trial: not reported Numbers in treatment/control treatment periods: 20 (assumed) Numbers completing trial: 20 (assumed) Age (range): 7-15 years; Age (mean): 10.7 (SD 2.7) M/F: 12/8 Asthma severity: moderate-severe Mean FEV1 (% pred): 60 (SD 15); mean duration of asthma: 8.6 years (SD 3.4) Inclusion criteria: 6-16 years of age; chronic asthma according to ATS criteria; FEV1 reversibility >/=20%; wheeze for at least 6 months; persistent wheeze with daily medication for symptomatic relief
Interventions	1. Xanthine (sustained release theophylline, serum theophylline level 10-20 mcg/mL) 2. Metaproteronol tablets (10mg per dose <60lbs; 20 mg per dose >60lbs) Study duration: 8 weeks (pre trial theophylline titration period of 2-4 weeks). No washout phase reported (carryover tests were not significant). Co-interventions: BDP: N = 5; SCG:N = 5; BDP+SCG: N = 1; alternate day OCS: N = 2
Outcomes	Symptoms; exacerbations; absence from school; rescue medication usage; am/pm/mid afternoon PEF; adverse effects
Notes	Predosing with study medication

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Unclear risk	Double-dummy
Incomplete outcome data addressed? All outcomes	Low risk	All participants completed
Free of other bias?	High risk	All participants exposed to xanthine in a pre-trial dose adjustment phase.

Rachelefsky 1986

Methods	Randomised, double-blind parallel group study. Withdrawals: 2. Jadad score: 3 Statistical analysis: Two group Student's t test
Participants	Numbers enrolled into trial: 22

Rachelefsky 1986 *(Continued)*

	Numbers in treatment/control treatment groups: 10/10 (2 withdrawals not analysed) Numbers completing trial: 20 Age (range): 6-12 years Age (mean): 9.8 (SD 2.1) M/F: 11/9 Asthma severity: Mild, asymptomatic Inclusion criteria: 6-12 years; mild asthma Exclusion criteria: Need for long-term oral medication; oral BDs in >/=6 months; oral anti-histamines/decongestants; learning disability/behavioural disorder
Interventions	1. Xanthine (sustained release theophylline serum level between 10 and 20mcg/mL) every 8-12 hours 2. Placebo Study duration: 2 week run-in and 4 week treatment period
Outcomes	Psychological tests (memory,attention span, spatial visualisation, IQ); patient behaviour; parent and teacher evaluated assessment; symptoms; medication usage; physician assessment of asthma control at week 2 and 4
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Unclear risk	Described as double-blind
Incomplete outcome data addressed? All outcomes	High risk	Participants who completed contributed to population analysed
Free of other bias?	Low risk	No pre-trial xanthine exposure phase

Reed 1998

Methods	Randomised parallel group trial. Withdrawals (of total trial population): Xanthine: 97; BDP: 86. ITT population. Jadad score: 4
Participants	Numbers enrolled into trial: 195 children/552 adults Numbers in treatment/control groups: Xanth: 363; BDP: 384 (numbers of children not reported) Numbers completing trial: 564 (total) Age (range, children): 6-17 years Age (mean): Not reported M/F (children): 122/73 Asthma severity: Mild-to-moderate Inclusion criteria: Adults and children (6-65 years); diagnosis of asthma, with dyspnoea, cough and wheeze; requirement for treatment with BD; considered by physicians to be candidates for continuous treatment; FEV1 >50% predicted within month prior to randomisation; reversibility >/= 15%

Reed 1998 *(Continued)*

	Exclusion criteria: Tobacco usage in previous 6 months/history of smoking > 5 pack years; ARI in last 3 weeks; systemic CS treatment in last month/more than 30 days in previous 2 years; xanthine andICS together more than 1 month in previous year; SCG treatment in previous 60 days; topical nasal CS in last 30 days; maintenance immunotherapy; Serious AEs to CS/xanthine; illness that would contraindicate CS treatment; ADD, behavioural disorder, legal or mental incapacity, mental retardation, history of alcohol or drug abuse, other psychologic/emotional disorders requiring treatment; history of any other illness or required medications increasing risk of adverse reaction to study drugs; pregnancy, lactation, not using reliable method of birth control (where appropriate)
Interventions	Xanth (slow release theophylline - 100-300mg BID) + placebo BDP versus placebo xanthine + BDP 336 mcg (2 puffs QID) Study duration: 12 months
Outcomes	FEV1; methacholine challenge; histopathology; ECG; Chest X-ray; symptoms; PEF; additional medication; absence from school; side effects; ophthalmic examination
Notes	Included as adults and children were recruited. Data not entered for pooled population estimates. 45% participants previously taken theophylline

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Double-dummy
Incomplete outcome data addressed? All outcomes	Unclear risk	Intention to treat population described as: 'All 747 patients who met the criteria for randomisation were included for analysis of efficacy outcomes.'
Free of other bias?	Low risk	No pre-trial xanthine exposure phase

Schuller 1982

Methods	Randomised, crossover study. Withdrawals: not reported. Jadad score: 2 Statistical analysis: T test
Participants	Numbers enrolled into trial: not reported Numbers in treatment/control treatment periods: 20 Numbers completing trial: 20 Age (range): 6-14 years Age (mean): Not reported M/F: 14/6 Asthma severity: Not reported Inclusion criteria: ATS defined asthma; 6-14 years; daily wheeze requiring constant medication; FEV1 and FEF25-75 <75% predicted with improvement >/=20% after 2 inhalations SABA Exclusion criteria: Presence of other illness; sensitive to SABA/methylxanthines; treatment with OCS/cromolyn

Schuller 1982 *(Continued)*

Interventions	1. Xanthine (oral theophylline 10-20 mcg/mL) + placebo SABA 2. SABA (metaproterenol, <60lbs 1 x 10mcg/day, >60lbs 2 x 10mcg/day) + placebo xanthine Study duration: 2 week run-in (theophylline adjustment period). 4 week treatment periods. No wash-out phase was reported.
Outcomes	FVC; FEV1; FEF25-75; PEF; pulse; BP; respiratory rates; symptoms; additional medication; absence from school; hospital visits; side-effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Unclear risk	Described as double-blind
Incomplete outcome data addressed? All outcomes	Unclear risk	Crossover study; data analysed from participants who completed all arms of treatment.
Free of other bias?	High risk	All participants exposed to xanthine in a pre-trial dose adjustment phase.

Slater Nancy 1991

Methods	Randomised, crossover study. Withdrawals: not reported. Jadad score: 2 Statistical analysis: not clear
Participants	Numbers enrolled into trial: not reported Numbers in treatment/control treatment periods: 20 Numbers completing trial: 18 Age (range): 6-12 years Age (mean): Not reported M/F: Not clear Asthma severity: Not reported Inclusion criteria: Not reported
Interventions	1. Xanthine (oral theophylline 14-25mg/kg/day) 2. Placebo Study duration: 2 week run-in (theophylline-free period). 4 week treatment periods. Wash-out phase not adequately reported.
Outcomes	Conners Revised scales (parent and teacher assessment)
Notes	Unpublished conference abstract

Risk of bias

Slater Nancy 1991 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Unclear risk	Information not available
Incomplete outcome data addressed? All outcomes	Unclear risk	Not enough information available to determine how many participants withdrew from randomisation
Free of other bias?	Unclear risk	Unclear whether pre-trial treatment phase undertaken

Springer 1985

Methods	Randomised, double-blind, double dummy, crossover trial. Methods of randomisation: Not described. Withdrawals: none described. Jadad score: 2 Statistical analysis: Paired t test
Participants	Numbers enrolled into trial: not reported Numbers in treatment/control treatment periods: 13 Numbers completing trial: 13 Age (range): 8-13 years Age (mean): 10.5 years M/F: 9/4 Asthma severity: Moderate Previous interventions included: xanthine (theophylline), CS with SABA prn Inclusion criteria: 8-13 years; perennial asthma; requiring continuous daily medication for at least 6 months. Exclusion criteria: Not requiring steroid therapy in previous 3 months; children deemed to be of 'unacceptably low intelligence'.
Interventions	1. Xanthine (slow release theophylline, serum level - 10-20mcg/mL) + placebo SCG 2. SCG 20mg QID, via MDI + placebo xanthine Study duration: 2 x 4 weeks (plus 2 day washout)
Outcomes	Symptoms; am/pm PEF; additional medication; psychological tests; exercise tests;
Notes	Previous medications included xanthine

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Unclear risk	Information not available
Blinding?	Low risk	Double-dummy

Springer 1985 *(Continued)*

All outcomes		
Incomplete outcome data addressed? All outcomes	Unclear risk	Not enough information available to determine how many participants withdrew from randomisation
Free of other bias?	Low risk	No pre-trial xanthine exposure phase

Strang 1960

Methods	Randomised crossover study. Withdrawals: all participants completed. The drugs were not identical in appearance, and parents were told that their children were being given them in order to see which was better. Jadad score: 2 Statistical test: Unclear
Participants	Numbers enrolled into trial: not reported Numbers in treatment/control treatment periods: 14 Numbers completing trial: 14 Age (range): 7-13 years Age (mean): Not reported M/F: Unclear Asthma severity: Severe Participants given ephedrine in case of exacerbation Inclusion criteria: Not clear. Parents said that their children had asthma attacks once every 4 weeks Exclusion criteria: Not reported.
Interventions	1. Xanthine (choline theophyllinate QID - 0.1g for children <10 years old, 0.2g children >10 years old) 2. Placebo (lactose) Participants given ephedrine prn Study duration: 3 month treatment arms No washout phase was described
Outcomes	FEV1; symptoms; adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	High risk	Open label
Incomplete outcome data addressed? All outcomes	Unclear risk	All participants completed the study

Strang 1960 *(Continued)*

Free of other bias?	Low risk	No pre-trial xanthine exposure phase

Süssmuth 2003

Methods	Randomised parallel group trial. Withdrawals: 3 participants withdrew (xanthine: 2, placebo:1). Jadad score: 4
Participants	Numbers randomised: 36 Numbers completing trial: 33 Age (range): 6-18 years Age (mean): 12.5 years M/F: 29/7 Asthma severity: Moderate Participants were on ICS (BUD: 18; FP: 18), SABA prn, Inclusion criteria: 8-13 years; perennial asthma; requiring continuous daily medication for at least 6 months. Exclusion criteria: Not requiring steroid therapy in previous 3 months; children deemed to be of 'unacceptably low intelligence'.
Interventions	1. Xanthine (slow release theophylline 100mg caps - 10mg/kg (up to maximum of 600mg/d) 2. Matching placebo preparation. ICS, SABA were continued Run-in period 6 weeks. Study duration 12 weeks.
Outcomes	Symptoms; PEF; RV; Blood samples; lymphocyte subpopulations
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Low risk	Conducted off-site
Blinding? All outcomes	Unclear risk	Identical placebo
Incomplete outcome data addressed? All outcomes	High risk	Data analysed from participants who completed all arms of treatment.
Free of other bias?	Low risk	No pre-trial xanthine exposure phase

Tinkelman 1993

Methods	Randomised parallel group trial. Withdrawals described. ITT population. Jadad score: 3
Participants	Numbers enrolled into trial: 195 Number in treatment group (Xanth)/control group (BDP): 93/102 Numbers of withdrawals or dropouts (Xanth/BDP): 24/26

Tinkelman 1993 *(Continued)*

	Numbers completing trial (Xanth/BDP): 69/76 Age (range): 6-17 years. Age (mean SD): Xanth: 11.9 (2.8); BDP: 11.9 (2.7) Sex (M/F): Xanth: 65/28; BDP: 57/45 FEV1: Xanthine: 2.06 (SEM 0.10); BDP: 2.07 (SEM 0.08) PC20: Xanthine: 3.5 (95%CI 2.1, 6); BDP: 5.2 (95%CI 3.3, 8.2); Prior Xanthine use (%): Xanthine: 48; BDP: 46 Inclusion criteria: Cough, dyspnoea and wheeze requiring intermittent/constant BD treatment; FEV1 >50% predicted; FEV1 15% reversibility post BD; asthma severe enough to cause symptoms on 'most days'; symptoms maintained adequately with BD only Exclusion criteria: Acute RI within 3 weeks; steroid treatment within previous month/>30 days in past 2 years; inhaled SCG within 60 days; smoked in last 6 months; intranasal CS; serious AEs following previous treatment with either CS or Xanth; pregnancy/lactation
Interventions	BDP: 336mcg/day + two placebo tablets/day versus Xanthine (theophylline) two tablets/day (dosage titrated to maintain optimum symptom control and blood level theophylline of 8-15mcg/mL + placebo inhaler. Study duration: 4 weeks
Outcomes	PEF; FEV1; symptoms; rescue medication usage; asthma exacerbations; absence from work/school; side-effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available. Randomisattion stratified by clinical centre
Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	Unclear risk	Double-dummy
Incomplete outcome data addressed? All outcomes	Low risk	Analysis of outcome intended to follow-up participants attending clinic between certain time points: 'Not all patients adhered to the prescribed schedule. Hence, for each outcome we analysed the distribution of days between initiation of study medication use and test performance. A window of acceptable days was established without knowledge of random drug assignment. Those patients who were not seen in this window were excluded from the analysis for that time point. Because of a limited number of patients at any one center, analyses accounting for possible center differences were not pursued. All analyses used all available information.'
Free of other bias?	Low risk	No pre-trial xanthine exposure phase

Volovitz 1994

Methods	Randomised parallel group study. Withdrawals: Xanth: 1, xanthine + ketotifen: 2; 0.5 xanthine: 1, placebo: 3. Jadad score: 4

Volovitz 1994 *(Continued)*

Participants	Numbers enrolled into trial: 62 Numbers in treatment/control treatment periods: Xanth: 15; xanthine + ket: 16; 0.5 xanthine + ket: 15; PLA: 16 Numbers completing trial: 55 Age (range): 4-14 years Age (mean): 10.5 (SD 2.5) M/F: 42/13 (OUT OF COMPLETERS) Asthma severity: moderately severe Interventions pre-baseline in all children: xanth (6-9 weeks); ß-2 agonists (5-7 weeks); OCS (0.3-0.6 weeks) Inclusion criteria: 4-14 years; perennial asthma requiring continuous medication
Interventions	1. Xanthine (slow release theophylline, BID, equating to 10-20mcg/mL) + placebo ketotifen 2. Xanthine (slow release theophylline, BID, equating to 10-20mcg/mL) + ketotifen (1mcg BID) 3. 0.5 (baseline dose) Xanthine + ketotifen (1mcg BID) 4. Placebo xanthine + placebo ketotifen Study duration: 12 weeks
Outcomes	Symptom scores; am and pm PEF; side effects; psychological evaluations
Notes	2 week baseline period (high dose xanthine)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available (blocks of 16)
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Unclear risk	Double-dummy; identical placebo
Incomplete outcome data addressed? All outcomes	High risk	Data used from participants who completed
Free of other bias?	High risk	All participants exposed to xanthine in a pre-trial dose adjustment phase.

Wilson 1982

Methods	Randomised, double-blind crossover trial. Method of randomisation: not reported; Blinding: identical placebo. Withdrawals: 16. Jadad score: 4 Statistical analysis: Diary scores analysed by paired t tests. Paired t tests used to compare symptoms during each drug period. PEF measured by ANOVA.
Participants	Numbers enrolled into trial: 40 Numbers in treatment/control treatment periods: 24 (16 withdrawals) Numbers completing trial: 24 Age (range): 5-14 years Age (mean): 9 years M/F: 15/9 Asthma severity: Not reported

Wilson 1982 *(Continued)*

	Co-administration of ß-agonists prn Inclusion criteria: School age children; requiring continuous treatment due to frequent symptoms (>10 days per month) or if already taking non-steroidal prophylactic medications; perennial asthma
Interventions	1. Xanthine (slow release theophylline, 14mg/kg) BID 2. Placebo Study duration: 2 x 8 week treatment periods. No washout phase reported.
Outcomes	Symptoms; am and pm PEF; additional medication usage; side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; information on sequence generation not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Unclear risk	Identical placebo
Incomplete outcome data addressed? All outcomes	Unclear risk	Crossover study; data analysed from participants who completed all arms of treatment
Free of other bias?	Low risk	No pre-trial xanthine exposure phase

ADD: Attention deficit disorder; BD: Bronchodilator; BDP: beclomethasone dipropionate; BID: twice daily; BP: Blood pressure; CS: corticosteroid; DIP: pmPEF - amPEF/pmPEF x 100; EIB: Exercise-induced bronchoconstriction; FEV1: Forced expiratory volume in 1 second; FP: Fluticasone propionate; MMEF: maximum mid-expiratory flow); PRN: as required; QID: four times daily; RV: Residual volume; SABA: short acting beta-agonist; SAL: salmeterol; SCG: sodium cromoglycate; URTI: upper respiratory tract infection; Xanth: xanthine

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alvarez Sintes 1995	Study duration <4 weeks
Avital 1991	Study period <4 weeks
Badiei 1975	Study conducted in children, but assessing the effects of theophylline in EIB
Bellia 1988	Study conducted in adults
Bender 1991	Non-randomised study
Bender 1992	Study duration < 4 weeks
Bierman 1975	Study conducted in EIB

Study	Reason for exclusion
Bierquist 1983	Study duration < 4 weeks
Boner 1984	Study conducted in EIB
Brune 1991	RCT conducted in adults
Bundgaard 1982	RCT conducted in adults
Bundgaard 1990	RCT - Study duration less than 4 weeks
Chapman 1989	RCT conducted in adults
Crimi 1987	Study conducted in adults
Crimi 1995	Study conducted in adults
Darke 1970	Controlled trial conducted in adult participants.
Edwards 1995	Study conducted in adults
Elias-Jones 1984	Study duration was less than 4 weeks.
Eriksson 1983	This RCT was conducted in adults and was conducted over a treatment period which was shorter than the stated entry criterion of 4 weeks.
Evans 1997	RCT conducted in adults
Fabbri 1996	Review article.
Furukawa 1988	Review article.
Furukawa 1988a	Study duration less than 4 weeks
Godley 1991	Prospective evaluation of dosing strategies in 36 children presenting to ED with acute asthma
Goldthorpe 1964	Before and after study assessing the effects of theophylline in all respiratory conditions.
Groggins 1980	RCT - Study duration less than 4 weeks
Guo 2002	RCT - Study compared xanthine as an additive treatment to ICS. This study was excluded due to the absence of a placebo control.
Haahtela 1998	Review article
Heimlich 1964	RCT - Study duration less than 4 weeks
Hendeles 1995	Study conducted in adults
Hoffmann-Streb 1993	Study done in EIB
Ibáñez 1994	Study was done in EIB
Irvin 2007	Study conducted in people >15 years of age
Jain 1993	RCT - Study duration less than 4 weeks.

Study	Reason for exclusion
Jatulis 1998	Cross-sectional survey
Johnson 1998	Review article.
Jonkman 1984	Non-randomised study in adults
Katz 1978	RCT - Study duration less than 4 weeks.
Koyande 1993	RCT - study duration less than 4 weeks.
Kreisman 1984	RCT - study duration less than 4 weeks.
Laursen 1985	RCT - study conducted in adults.
Lönnerholm 1981	RCT - study duration was less than 4 weeks.
Marín 1990	RCT - study conducted in adults
Muir 1992	RCT - inadequate control group for this review
Nicholson 1979	RCT - study of less than 4 weeks.
Paggiaro 1996	RCT - study conducted in adults
Pastorello 1998	RCT - study conducted in adults
Pedersen 1985	RCT - study duration less than 4 weeks
Pednekar 1998	Study conducted in adults, comparing theophylline with salmeterol
Pereira 1988	RCT - sudy conducted in acute asthma
Pijaskic-Kamenov 2001	This RCT assessing the additive effect of xanthine to inhaled in FP in paediatric asthma did not meet the inclusion criteria of the review in the absence of a placebo control.
Rachelfsky 1978	RCT - study duration less than 4 weeks
Rappaport 1989	RCT - study duration less than 4 weeks
Roberts 1986	RCT - study duration less than 4 weeks
Roberts 2003	RCT conducted in severe acute asthma
Roddick 1979	RCT - study duration less than 4 weeks
Schlieper 1991	RCT - study duration less than 4 weeks
Schnabel 1989	RCT - study duration less than 4 weeks
Shaffer 1997	Review article
Sienra Monge 1994	RCT - conducted in acute asthma
Stein 1993	RCT - study duration less than 4 weeks

Study	Reason for exclusion
Sullivan 1994	Study conducted in adults.
Trakultivakorn 1999	This crossover RCT of two different xanthine agents compared with placebo was conducted in children, but we excluded it due to its short term duration.
Ukena 1998	Study conducted in adults.
Van Asperen 1981	RCT - study duration less than 4 weeks.
Van Caillie 1988	Cross-over study assessing only short-term (i.e. acute efffects) of xanthine compared with oral beta2 agonists. RCT - study duration less than 4 weeks.
Vilkka 1990	RCT - study duration less than 4 weeks.
Ward 1993	Study conducted in adult asthmatics
Weinberger 1974	RCT - study duration less than 4 weeks.
Wheatley 1982	Study conducted in adult asthmatics
Youngchaiyud 1995	Study conducted in adult asthmatics
Zeitlin 1988	Although described as a crossover study, the authors do not mention that the order of treatments was randomised, and nor do they give the duration of the study. Control EEGs were conducted in asthmatic children who were not recruited to the study.

RCT - randomised controlled trial; EIB: Exercise-induced bronchoconstriction or asthma

DATA AND ANALYSES

Comparison 1. Xanthine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom free days (24 hours - crossover studies)	3		% (Fixed, 95% CI)	7.97 [3.41, 12.53]
2 Symptom-free days (crossover studies)	2		% (Fixed, 95% CI)	12.82 [-1.96, 27.61]
3 Symptom free nights (crossover studies)	4		% (Fixed, 95% CI)	10.60 [4.17, 17.03]
4 Symptom free days - wheeze (crossover studies)	2		% (Fixed, 95% CI)	4.70 [-7.54, 16.95]
5 Symptom free days - actvity (crossover studies)	1		% (Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6 Symptom free days - cough (crossover studies)	2		% (Fixed, 95% CI)	8.30 [-5.72, 22.31]
7 Change in symptom free days (% - parallel studies)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8 Total symptom score (SMD - crossover studies)	3		SD units (Fixed, 95% CI)	-0.41 [-0.62, -0.19]
9 Day symptom score (SMD; estimated SD - crossover studies)	7		SD units (Fixed, 95% CI)	-0.32 [-0.51, -0.14]
9.1 Available estimate of variance	6		SD units (Fixed, 95% CI)	-0.38 [-0.58, -0.18]
9.2 Missing estimate of variance	1		SD units (Fixed, 95% CI)	0.02 [-0.47, 0.51]
10 Symptom score (night time - SMD; estimated SD)	7	246	SD units (Fixed, 95% CI)	-0.44 [-0.62, -0.27]
10.1 Available estimate of variance	6	214	SD units (Fixed, 95% CI)	-0.48 [-0.66, -0.29]
10.2 Missing estimate of variance	1	32	SD units (Fixed, 95% CI)	-0.22 [-0.71, 0.27]
11 Symptom score (cough - SMD)	2		SD units (Fixed, 95% CI)	-0.38 [-0.71, -0.05]
12 Symptom score (activity - SMD)	1		SD units (Fixed, 95% CI)	Totals not selected
13 Hospitalisation (crossover studies)	5	168	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.37, 1.91]
14 Severe attacks of asthma (crossover studies)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
15 Number of patients requiring oral steroids (crossover studies)	2	62	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.21, 4.68]
16 Days when hospital admission nec-essary	0		% (Fixed, 95% CI)	Totals not selected
17 Days when no additional pred-nisolone given	0		% (Fixed, 95% CI)	Totals not selected
18 Acute attacks of asthma (crossover studies)	1		ex'cbtions/pat (Fixed, 95% CI)	Totals not selected
19 Additional beta2-agonist use (crossover studies)	8		puffs/day (Fixed, 95% CI)	-0.41 [-0.56, -0.26]
19.1 Available estimates of variance	6		puffs/day (Fixed, 95% CI)	-0.41 [-0.57, -0.26]
19.2 Missing estimates of variance	2		puffs/day (Fixed, 95% CI)	-0.41 [-0.92, 0.10]
20 Days when no salbutamol given	0		% (Fixed, 95% CI)	Totals not selected
21 FEV1 (crossover studies)	1		Litres (Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22 FEV1 (predicted - crossover studies)	2		% (Fixed, 95% CI)	8.75 [0.80, 16.69]
23 Morning PEF (predicted - crossover studies)	3		% (Fixed, 95% CI)	5.22 [2.91, 7.52]
24 Morning PEF (Litres - crossover studies)	2		L/min (Fixed, 95% CI)	33.60 [14.63, 52.57]
25 Evening PEF (predicted - crossover studies)	3		% (Fixed, 95% CI)	4.05 [2.47, 5.62]
26 Evening PEF (Litres - crossover studies)	2		L/min (Fixed, 95% CI)	26.66 [15.51, 37.80]
27 Clinic PEF (predicted - crossover studies)	1		% (Fixed, 95% CI)	Totals not selected
28 Clinic PEF (Litres - crossover studies)	1		L/min (Fixed, 95% CI)	Totals not selected
29 PEF (days when PEF < 50% predicted - crossover studies)	0		% (Fixed, 95% CI)	Totals not selected
30 PEF (diurnal variation - crossover studies)	0		% (Fixed, 95% CI)	Totals not selected
31 Side effects (any - crossover studies)	4	134	Odds Ratio (M-H, Fixed, 95% CI)	4.48 [1.65, 12.19]
32 Headache (crossover studies)	2	66	Odds Ratio (M-H, Fixed, 95% CI)	3.20 [0.32, 32.41]
33 Withdrawal from trial (parallel group/first arm data)	2	48	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.28, 3.82]
34 Teacher behavioural assessment score (parallel groups)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
35 Conner's revised scale	1		Conners (Fixed, 95% CI)	Totals not selected
35.1 Parental assessment	1		Conners (Fixed, 95% CI)	0.0 [0.0, 0.0]
35.2 Teacher assessment	1		Conners (Fixed, 95% CI)	0.0 [0.0, 0.0]
36 Sleep disturbance (crossover studies)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
37 Abdominal pain, nausea or vomiting (crossover studies)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Xanthine versus placebo, Outcome 1 Symptom free days (24 hours - crossover studies).

Study or subgroup	Xanthine N	Placebo N	% (SE)	% IV, Fixed, 95% CI	Weight	% IV, Fixed, 95% CI
Chow 1989	24	24	8.8 (5.26)		19.54%	8.8[-1.51,19.11]
Edmunds 1980	30	30	8 (7.76)		8.98%	8[-7.21,23.21]
Pedersen 1983	19	19	7.7 (2.75)		71.48%	7.74[2.35,13.13]
Total (95% CI)					**100%**	**7.97[3.41,12.53]**
Heterogeneity: Tau^2=0; Chi^2=0.03, df=2(P=0.98); I^2=0%						
Test for overall effect: Z=3.43(P=0)						

Analysis 1.2. Comparison 1 Xanthine versus placebo, Outcome 2 Symptom-free days (crossover studies).

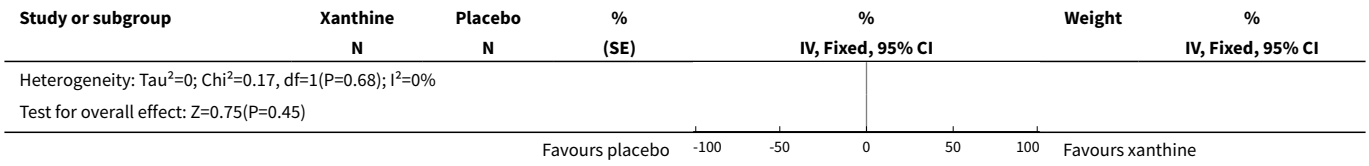
Study or subgroup	Xanthine N	Placebo N	% (SE)	% IV, Fixed, 95% CI	Weight	% IV, Fixed, 95% CI
Levene 1986	14	14	12.7 (9.78)		59.48%	12.7[-6.47,31.87]
Wilson 1982	24	24	13 (11.85)		40.52%	13[-10.23,36.23]
Total (95% CI)					**100%**	**12.82[-1.96,27.61]**
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.98); I^2=0%						
Test for overall effect: Z=1.7(P=0.09)						

Analysis 1.3. Comparison 1 Xanthine versus placebo, Outcome 3 Symptom free nights (crossover studies).

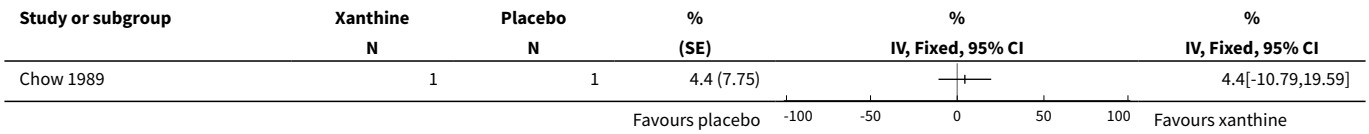
Study or subgroup	Xanthine N	Placebo N	% (SE)	% IV, Fixed, 95% CI	Weight	% IV, Fixed, 95% CI
Chow 1989	24	24	13.9 (7.69)		18.21%	13.9[-1.17,28.97]
Levene 1986	15	15	11.7 (6.52)		25.34%	11.7[-1.08,24.48]
Nolan 1982	11	11	5.7 (5.93)		30.63%	5.7[-5.92,17.32]
Wilson 1982	24	24	13 (6.458)		25.82%	13[0.34,25.66]
Total (95% CI)					**100%**	**10.6[4.17,17.03]**
Heterogeneity: Tau^2=0; Chi^2=1.03, df=3(P=0.79); I^2=0%						
Test for overall effect: Z=3.23(P=0)						

Analysis 1.4. Comparison 1 Xanthine versus placebo, Outcome 4 Symptom free days - wheeze (crossover studies).

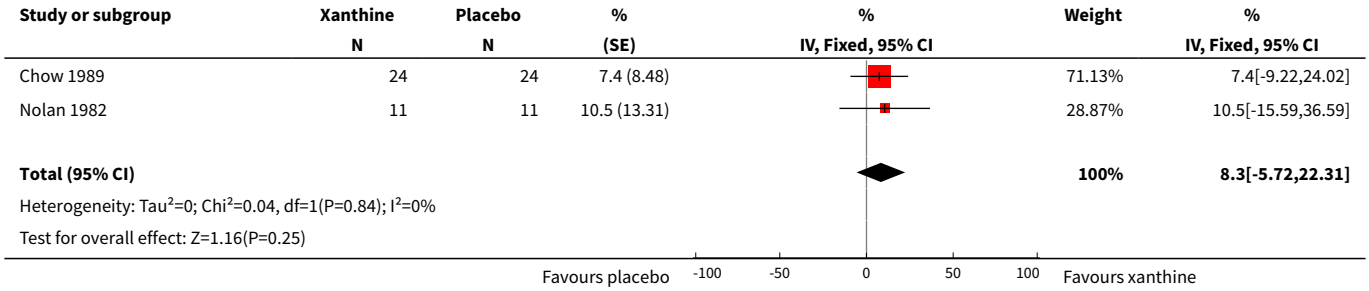
Study or subgroup	Xanthine N	Placebo N	% (SE)	% IV, Fixed, 95% CI	Weight	% IV, Fixed, 95% CI
Chow 1989	24	24	7.4 (9.1)		47.12%	7.4[-10.44,25.24]
Nolan 1982	11	11	2.3 (8.59)		52.88%	2.3[-14.54,19.14]
Total (95% CI)					**100%**	**4.7[-7.54,16.95]**



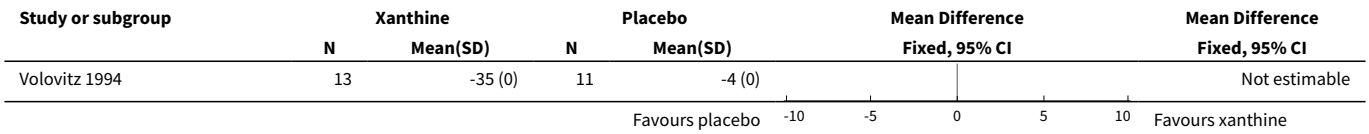
Analysis 1.5. Comparison 1 Xanthine versus placebo, Outcome 5 Symptom free days - actvity (crossover studies).



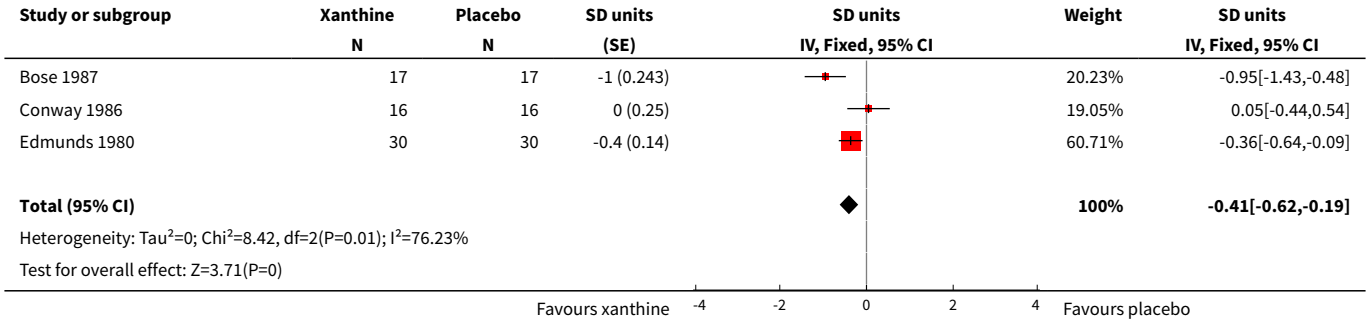
Analysis 1.6. Comparison 1 Xanthine versus placebo, Outcome 6 Symptom free days - cough (crossover studies).



Analysis 1.7. Comparison 1 Xanthine versus placebo, Outcome 7 Change in symptom free days (% - parallel studies).

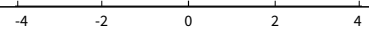


Analysis 1.8. Comparison 1 Xanthine versus placebo, Outcome 8 Total symptom score (SMD - crossover studies).



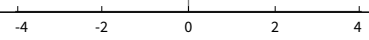
Analysis 1.9. Comparison 1 Xanthine versus placebo, Outcome 9 Day symptom score (SMD; estimated SD - crossover studies).

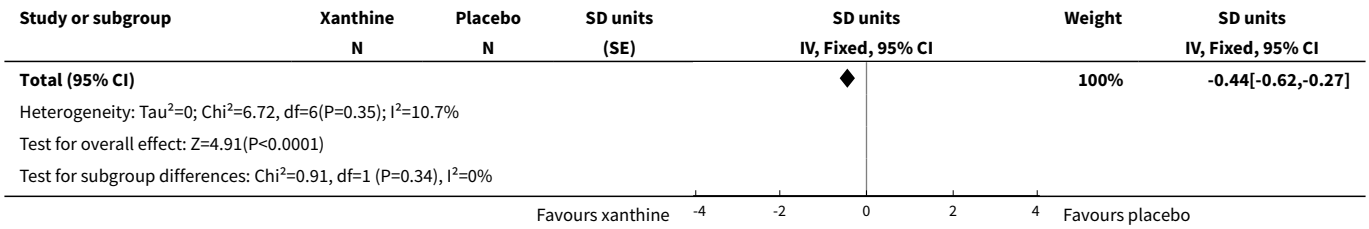
Study or subgroup	Xanthine N	Placebo N	SD units (SE)	SD units IV, Fixed, 95% CI	Weight	SD units IV, Fixed, 95% CI
1.9.1 Available estimate of variance						
Bose 1987	17	17	-0.7 (0.243)		15.17%	-0.73[-1.21,-0.25]
Chow 1989	24	24	-0.4 (0.204)		21.43%	-0.41[-0.81,-0.01]
Conway 1986	16	16	0 (0.25)		14.27%	0.03[-0.46,0.52]
Levene 1986	14	14	-0.3 (0.267)		12.51%	-0.27[-0.79,0.25]
Nolan 1982	11	11	-0.1 (0.267)		12.51%	-0.14[-0.66,0.39]
Wilson 1982	11	11	-0.8 (0.301)		9.84%	-0.81[-1.4,-0.22]
Subtotal (95% CI)					**85.73%**	**-0.38[-0.58,-0.18]**
Heterogeneity: Tau^2=0; Chi^2=7.86, df=5(P=0.16); I^2=36.36%						
Test for overall effect: Z=3.71(P=0)						
1.9.2 Missing estimate of variance						
Glass 1981	16	16	0 (0.25)		14.27%	0.02[-0.47,0.51]
Subtotal (95% CI)					**14.27%**	**0.02[-0.47,0.51]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.08(P=0.93)						
Total (95% CI)					**100%**	**-0.32[-0.51,-0.14]**
Heterogeneity: Tau^2=0; Chi^2=10.04, df=6(P=0.12); I^2=40.26%						
Test for overall effect: Z=3.41(P=0)						
Test for subgroup differences: Chi^2=2.19, df=1 (P=0.14), I^2=54.27%						



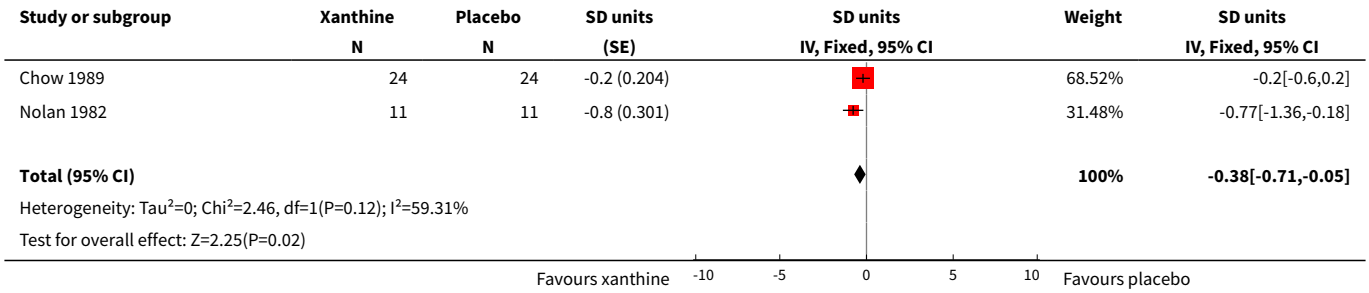
Analysis 1.10. Comparison 1 Xanthine versus placebo, Outcome 10 Symptom score (night time - SMD; estimated SD).

Study or subgroup	Xanthine N	Placebo N	SD units (SE)	SD units IV, Fixed, 95% CI	Weight	SD units IV, Fixed, 95% CI
1.10.1 Available estimate of variance						
Bose 1987	17	17	-0.9 (0.24)		14.05%	-0.88[-1.35,-0.41]
Chow 1989	24	24	-0.5 (0.204)		19.45%	-0.55[-0.95,-0.15]
Conway 1986	16	16	-0.1 (0.25)		12.95%	-0.08[-0.57,0.41]
Levene 1986	15	15	-0.5 (0.258)		12.16%	-0.52[-1.03,-0.01]
Nolan 1982	11	11	-0.3 (0.3)		8.99%	-0.34[-0.93,0.25]
Wilson 1982	24	24	-0.4 (0.204)		19.45%	-0.41[-0.81,-0.01]
Subtotal (95% CI)					**87.05%**	**-0.48[-0.66,-0.29]**
Heterogeneity: Tau^2=0; Chi^2=5.81, df=5(P=0.32); I^2=13.97%						
Test for overall effect: Z=4.93(P<0.0001)						
1.10.2 Missing estimate of variance						
Glass 1981	16	16	-0.2 (0.25)		12.95%	-0.22[-0.71,0.27]
Subtotal (95% CI)					**12.95%**	**-0.22[-0.71,0.27]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.88(P=0.38)						

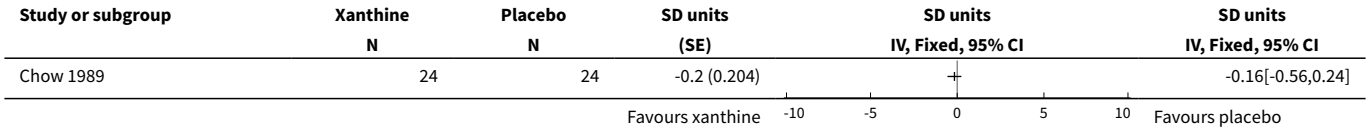




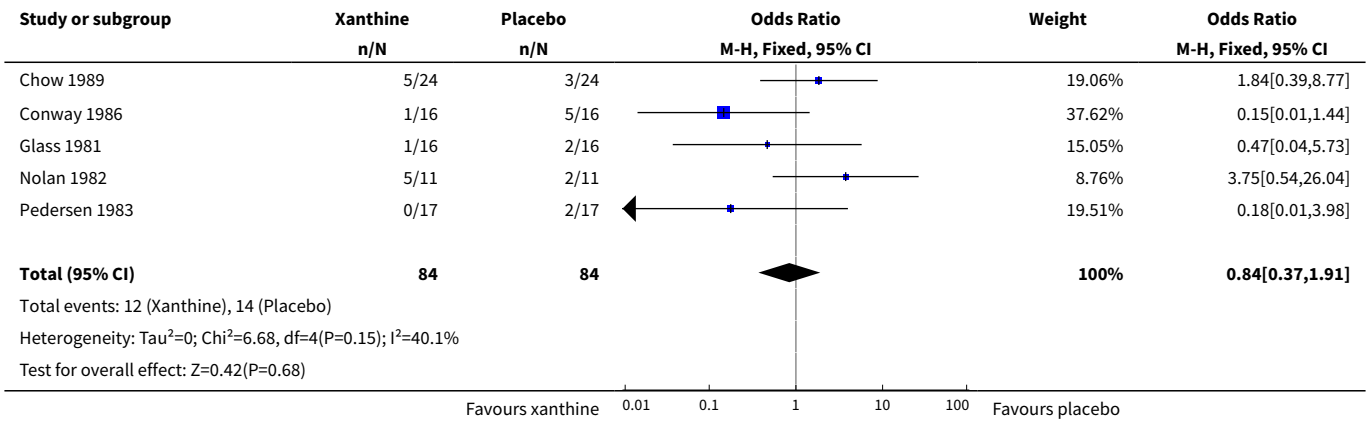
Analysis 1.11. Comparison 1 Xanthine versus placebo, Outcome 11 Symptom score (cough - SMD).



Analysis 1.12. Comparison 1 Xanthine versus placebo, Outcome 12 Symptom score (activity - SMD).



Analysis 1.13. Comparison 1 Xanthine versus placebo, Outcome 13 Hospitalisation (crossover studies).



Analysis 1.14. Comparison 1 Xanthine versus placebo, Outcome 14 Severe attacks of asthma (crossover studies).

Study or subgroup	Xanthine n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Edmunds 1980	2/30	8/30		0.2[0.04,1.02]

Favours xanthine 0.001 0.1 1 10 1000 Favours placebo

Analysis 1.15. Comparison 1 Xanthine versus placebo, Outcome 15 Number of patients requiring oral steroids (crossover studies).

Study or subgroup	Xanthine n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Glass 1981	0/16	2/16		75.21%	0.18[0.01,3.97]
Levene 1986	3/15	1/15		24.79%	3.5[0.32,38.23]
Total (95% CI)	**31**	**31**		**100%**	**1[0.21,4.68]**
Total events: 3 (Xanthine), 3 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.25, df=1(P=0.13); I^2=55.55%					
Test for overall effect: Not applicable					

Favours xanthine 0.01 0.1 1 10 100 Favours placebo

Analysis 1.18. Comparison 1 Xanthine versus placebo, Outcome 18 Acute attacks of asthma (crossover studies).

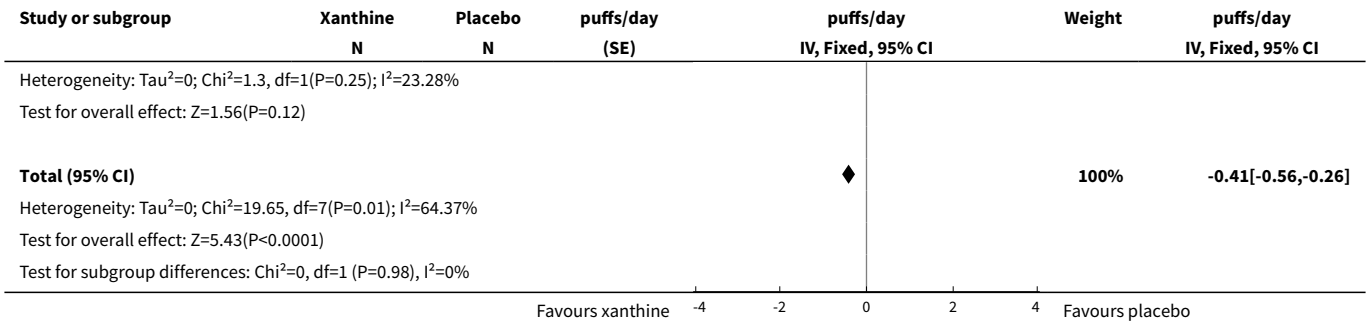
Study or subgroup	Xanthine N	Placebo N	ex'cbtions/pat (SE)	ex'cbtions/pat IV, Fixed, 95% CI	ex'cbtions/pat IV, Fixed, 95% CI
Pedersen 1983	19	19	-1.4 (3.64)		-1.44[-8.57,5.7]

Favours xanthine -10 -5 0 5 10 Favours placebo

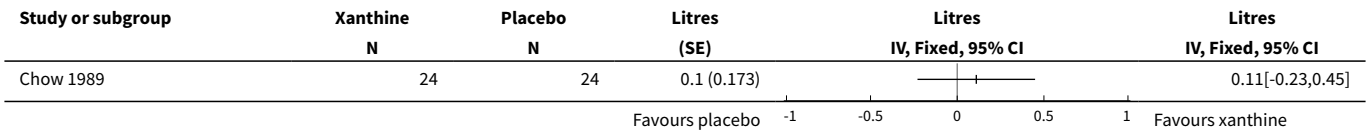
Analysis 1.19. Comparison 1 Xanthine versus placebo, Outcome 19 Additional beta2-agonist use (crossover studies).

Study or subgroup	Xanthine N	Placebo N	puffs/day (SE)	puffs/day IV, Fixed, 95% CI	Weight	puffs/day IV, Fixed, 95% CI
1.19.1 Available estimates of variance						
Bose 1987	17	17	-11.1 (3.06)		0.06%	-11.1[-17.1,-5.1]
Edmunds 1980	30	30	-0.3 (0.092)		67.96%	-0.32[-0.5,-0.14]
Levene 1986	7	7	-0.8 (0.29)		6.88%	-0.78[-1.35,-0.21]
Nolan 1982	11	11	-1.8 (0.93)		0.67%	-1.8[-3.62,0.02]
Pedersen 1983	16	16	-0.7 (0.254)		9.01%	-0.7[-1.2,-0.2]
Wilson 1982	24	24	-0.4 (0.29)		6.88%	-0.37[-0.94,0.2]
Subtotal (95% CI)					**91.47%**	**-0.41[-0.57,-0.26]**
Heterogeneity: Tau^2=0; Chi^2=18.34, df=5(P=0); I^2=72.74%						
Test for overall effect: Z=5.2(P<0.0001)						
1.19.2 Missing estimates of variance						
Chow 1989	24	24	-0.6 (0.311)		5.99%	-0.6[-1.21,0.01]
Glass 1981	16	16	0.1 (0.477)		2.55%	0.05[-0.88,0.98]
Subtotal (95% CI)					**8.53%**	**-0.41[-0.92,0.1]**

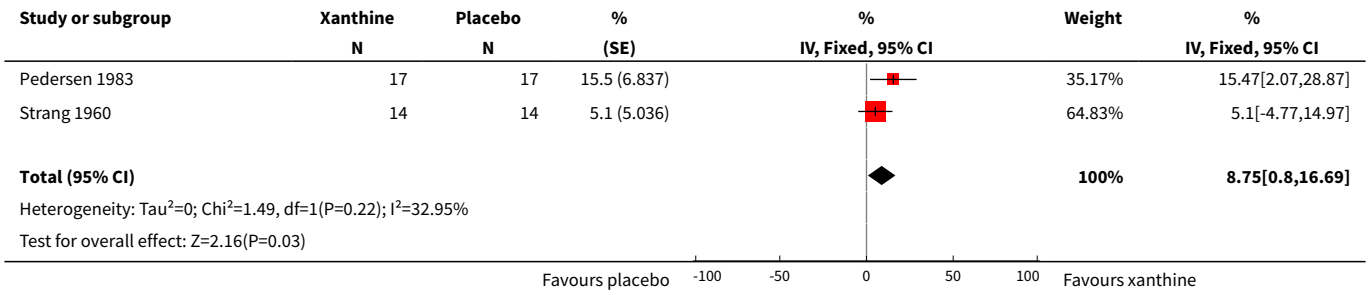
Favours xanthine -4 -2 0 2 4 Favours placebo



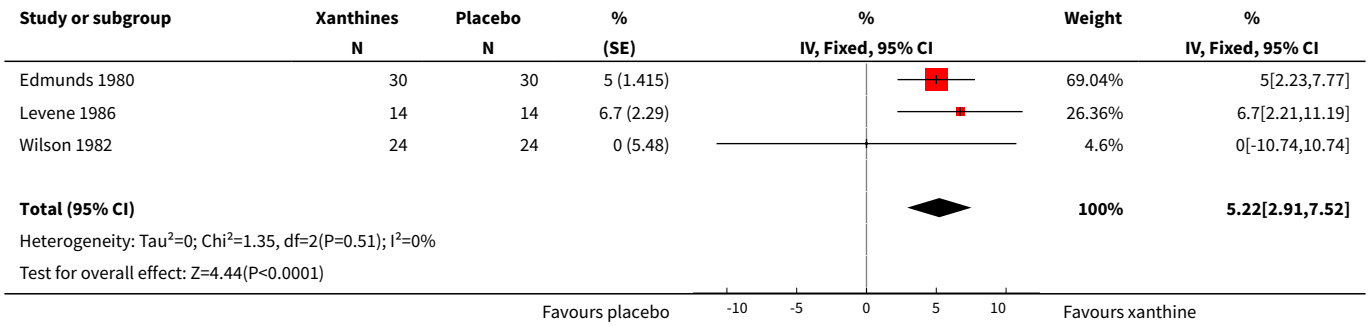
Analysis 1.21. Comparison 1 Xanthine versus placebo, Outcome 21 FEV1 (crossover studies).



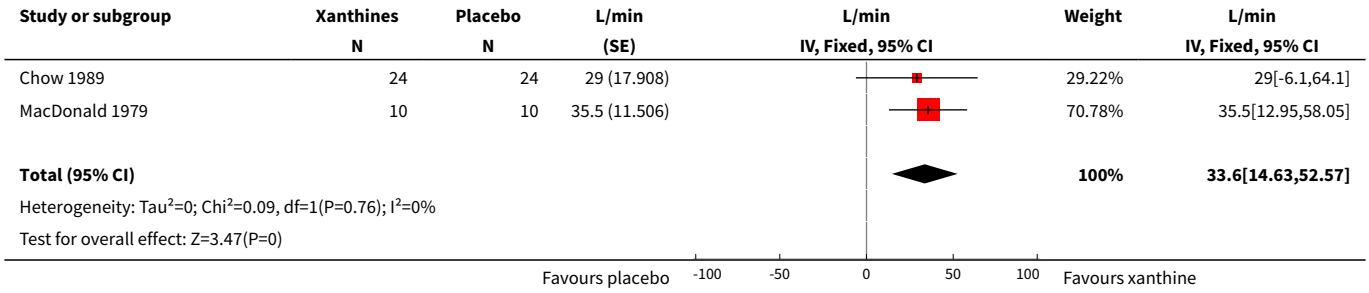
Analysis 1.22. Comparison 1 Xanthine versus placebo, Outcome 22 FEV1 (predicted - crossover studies).



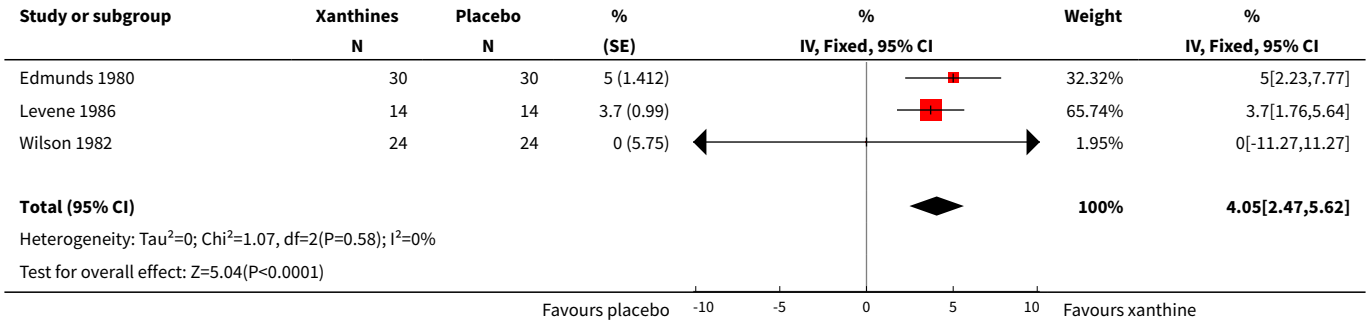
Analysis 1.23. Comparison 1 Xanthine versus placebo, Outcome 23 Morning PEF (predicted - crossover studies).



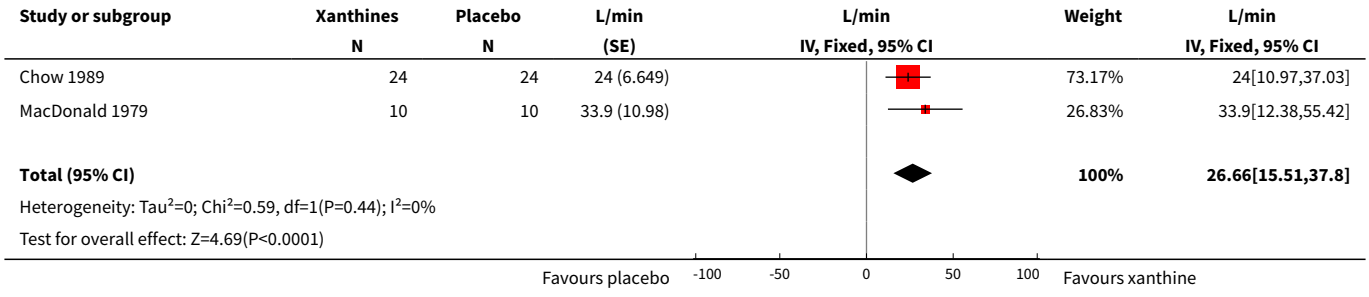
Analysis 1.24. Comparison 1 Xanthine versus placebo, Outcome 24 Morning PEF (Litres - crossover studies).



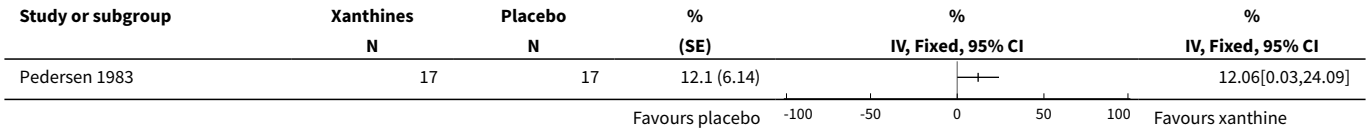
Analysis 1.25. Comparison 1 Xanthine versus placebo, Outcome 25 Evening PEF (predicted - crossover studies).



Analysis 1.26. Comparison 1 Xanthine versus placebo, Outcome 26 Evening PEF (Litres - crossover studies).

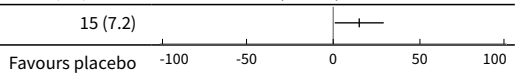


Analysis 1.27. Comparison 1 Xanthine versus placebo, Outcome 27 Clinic PEF (predicted - crossover studies).



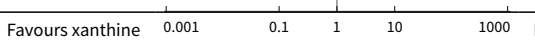
Analysis 1.28. Comparison 1 Xanthine versus placebo, Outcome 28 Clinic PEF (Litres - crossover studies).

Study or subgroup	Xanthines N	Placebo N	L/min (SE)	L/min IV, Fixed, 95% CI	L/min IV, Fixed, 95% CI
Chow 1989	24	24	15 (7.2)		15[0.89,29.11]



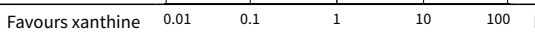
Analysis 1.31. Comparison 1 Xanthine versus placebo, Outcome 31 Side effects (any - crossover studies).

Study or subgroup	Xanthine n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Bose 1987	3/17	0/17		10.02%	8.45[0.4,177.29]
Levene 1986	2/15	0/15		10.49%	5.74[0.25,130.37]
Nolan 1982	7/11	1/11		9.04%	17.5[1.6,191.89]
Wilson 1982	7/24	4/24		70.45%	2.06[0.51,8.25]
Total (95% CI)	**67**	**67**		**100%**	**4.48[1.65,12.19]**
Total events: 19 (Xanthine), 5 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.64, df=3(P=0.45); I^2=0%					
Test for overall effect: Z=2.94(P=0)					



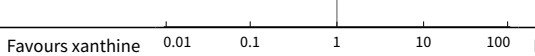
Analysis 1.32. Comparison 1 Xanthine versus placebo, Outcome 32 Headache (crossover studies).

Study or subgroup	Xanthine n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Bose 1987	1/20	0/20		50.98%	3.15[0.12,82.16]
Levene 1986	1/13	0/13		49.02%	3.24[0.12,87.13]
Total (95% CI)	**33**	**33**		**100%**	**3.2[0.32,32.41]**
Total events: 2 (Xanthine), 0 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=0.98(P=0.33)					



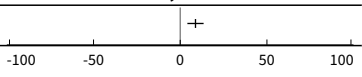
Analysis 1.33. Comparison 1 Xanthine versus placebo, Outcome 33 Withdrawal from trial (parallel group/first arm data).

Study or subgroup	Xanthine n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Gil 1993	8/12	4/9		34.53%	2.5[0.42,14.83]
Volovitz 1994	1/14	3/13		65.47%	0.26[0.02,2.85]
Total (95% CI)	**26**	**22**		**100%**	**1.03[0.28,3.82]**
Total events: 9 (Xanthine), 7 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.23, df=1(P=0.14); I^2=55.22%					
Test for overall effect: Z=0.05(P=0.96)					



Analysis 1.34. Comparison 1 Xanthine versus placebo, Outcome 34 Teacher behavioural assessment score (parallel groups).

Study or subgroup	Xanthine N	Xanthine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Rachelefsky 1986	10	5.3 (5.9)	10	-3.5 (4.7)		8.8[4.12,13.48]

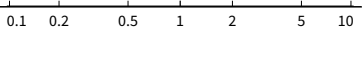


Analysis 1.35. Comparison 1 Xanthine versus placebo, Outcome 35 Conner's revised scale.

Study or subgroup	Xanthine N	Placebo N	Conners (SE)	Conners IV, Fixed, 95% CI	Conners IV, Fixed, 95% CI
1.35.1 Parental assessment					
Slater Nancy 1991	13	13	0.1 (0.55)		0.06[-1.02,1.14]
1.35.2 Teacher assessment					
Slater Nancy 1991	13	13	0.2 (0.32)		0.17[-0.46,0.8]

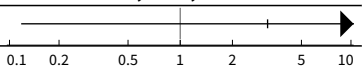
Analysis 1.36. Comparison 1 Xanthine versus placebo, Outcome 36 Sleep disturbance (crossover studies).

Study or subgroup	Xanthine n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Levene 1986	1/13	0/13		3.24[0.12,87.13]



Analysis 1.37. Comparison 1 Xanthine versus placebo, Outcome 37 Abdominal pain, nausea or vomiting (crossover studies).

Study or subgroup	Xanthine n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Glass 1981	1/16	0/16		3.19[0.12,84.43]



Comparison 2. Xanthine versus inhaled corticosteroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom score slopes (parallel studies)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Symptoms - wheeze (parallel studies)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Symptoms - shortness of breath (parallel studies)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Symptoms - cough (parallel studies)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Symptoms - activity tolerated (parallel studies)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 Nocturnal symptoms (parallel studies)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 Number of patients helped by medication (parallel studies)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Patients with more than one exacerbation (parallel studies)	2	271	Odds Ratio (M-H, Fixed, 95% CI)	2.87 [1.30, 6.36]
9 Patients needing at least one course of systemic glucocorticoid treatment (parallel studies)	2	267	Odds Ratio (M-H, Fixed, 95% CI)	3.10 [1.78, 5.41]
10 Additional systemic steroid use (parallel studies)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11 Additional beta2-agonist use (parallel studies)	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Parallel group	2	209	Odds Ratio (M-H, Fixed, 95% CI)	1.61 [0.92, 2.82]
12 FEV1 % predicted - post bronchodilator use (parallel studies)	2	321	Mean Difference (IV, Fixed, 95% CI)	-2.54 [-6.85, 1.77]
13 PEF % predicted - daily (parallel studies)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
14 Morning PEF % predicted (parallel studies)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15 FEF25-75 (parallel studies)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
16 Growth rate observed minus predicted (parallel studies)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
17 Total problems after one year (summary score for the Child Behaviour Checklist - parallel studies)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
18 Side effects (headache - parallel studies)	2	286	Odds Ratio (M-H, Fixed, 95% CI)	1.76 [1.09, 2.83]
19 Side effects (tremors - parallel studies)	2	286	Odds Ratio (M-H, Fixed, 95% CI)	1.48 [0.53, 4.14]

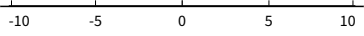
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20 Side effects (nausea - parallel studies)	2	286	Odds Ratio (M-H, Fixed, 95% CI)	1.98 [1.16, 3.40]
21 Withdrawal from study (parallel studies)	2	271	Odds Ratio (M-H, Random, 95% CI)	1.85 [0.47, 7.20]
22 Withdrawal due to lack of benefit (parallel studies)	2	271	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.54, 1.90]
23 Withdrawal from study due to adverse effect (parallel studies)	2	286	Odds Ratio (M-H, Fixed, 95% CI)	1.60 [0.37, 6.80]
24 Withdrawal due to exacerbation (parallel studies)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Xanthine versus inhaled corticosteroids, Outcome 1 Symptom score slopes (parallel studies).

Study or subgroup	Xanthines N	Xanthines Mean(SD)	ICS N	ICS Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Tinkelman 1993	69	-0.1 (1.2)	81	-0.7 (1.6)		0.59[0.14,1.04]

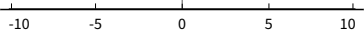
Analysis 2.2. Comparison 2 Xanthine versus inhaled corticosteroids, Outcome 2 Symptoms - wheeze (parallel studies).

Study or subgroup	Xanthine N	Xanthine Mean(SD)	ICS N	ICS Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Meltzer 1992	39	0.5 (0)	37	0.2 (0)		Not estimable



Analysis 2.3. Comparison 2 Xanthine versus inhaled corticosteroids, Outcome 3 Symptoms - shortness of breath (parallel studies).

Study or subgroup	Xanthine N	Xanthine Mean(SD)	ICS N	ICS Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Meltzer 1992	39	0.4 (0)	37	0.2 (0)		Not estimable



Analysis 2.4. Comparison 2 Xanthine versus inhaled corticosteroids, Outcome 4 Symptoms - cough (parallel studies).

Study or subgroup	Xanthines N	Xanthines Mean(SD)	ICS N	ICS Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Meltzer 1992	39	0.5 (0)	37	0.3 (0)		Not estimable

Favours xanthine -10 -5 0 5 10 Favours ICS

Analysis 2.5. Comparison 2 Xanthine versus inhaled corticosteroids, Outcome 5 Symptoms - activity tolerated (parallel studies).

Study or subgroup	Xanthine N	Xanthine Mean(SD)	ICS N	ICS Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Meltzer 1992	39	0.3 (0)	37	0.1 (0)		Not estimable

Favours xanthine -10 -5 0 5 10 Favours ICS

Analysis 2.6. Comparison 2 Xanthine versus inhaled corticosteroids, Outcome 6 Nocturnal symptoms (parallel studies).

Study or subgroup	Xanthine N	Xanthine Mean(SD)	ICS N	ICS Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Meltzer 1992	39	0.4 (0)	37	0.2 (0)		Not estimable

Favours xanthine -10 -5 0 5 10 Favours ICS

Analysis 2.7. Comparison 2 Xanthine versus inhaled corticosteroids, Outcome 7 Number of patients helped by medication (parallel studies).

Study or subgroup	Xanthine n/N	ICS n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Meltzer 1992	19/39	29/37		0.26[0.1,0.71]

Favours ICS 0.01 0.1 1 10 100 Favours xanthine

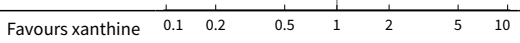
Analysis 2.8. Comparison 2 Xanthine versus inhaled corticosteroids, Outcome 8 Patients with more than one exacerbation (parallel studies).

Study or subgroup	Xanthine n/N	ICS n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Meltzer 1992	13/39	5/37		44.86%	3.2[1.01,10.15]
Tinkelman 1993	11/93	5/102		55.14%	2.6[0.87,7.8]
Total (95% CI)	**132**	**139**		**100%**	**2.87[1.3,6.36]**
Total events: 24 (Xanthine), 10 (ICS)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.06$, df=1(P=0.8); $I^2=0\%$					
Test for overall effect: Z=2.6(P=0.01)					

Favours xanthine 0.1 0.2 0.5 1 2 5 10 Favours ICS

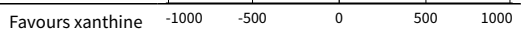
Analysis 2.9. Comparison 2 Xanthine versus inhaled corticosteroids, Outcome 9 Patients needing at least one course of systemic glucocorticoid treatment (parallel studies).

Study or subgroup	Xanthine n/N	ICS n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Meltzer 1992	18/35	6/37		19.77%	5.47[1.83,16.39]
Tinkelman 1993	34/93	19/102		80.23%	2.52[1.31,4.84]
Total (95% CI)	**128**	**139**		**100%**	**3.1[1.78,5.41]**
Total events: 52 (Xanthine), 25 (ICS)					
Heterogeneity: Tau^2=0; Chi^2=1.42, df=1(P=0.23); I^2=29.58%					
Test for overall effect: Z=3.98(P<0.0001)					



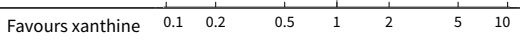
Analysis 2.10. Comparison 2 Xanthine versus inhaled corticosteroids, Outcome 10 Additional systemic steroid use (parallel studies).

Study or subgroup	Xanthine N	Xanthine Mean(SD)	ICS N	ICS Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Tinkelman 1993	93	123.9 (228.7)	102	58.4 (165)		65.5[9.06,121.94]



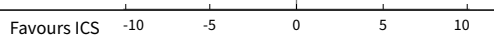
Analysis 2.11. Comparison 2 Xanthine versus inhaled corticosteroids, Outcome 11 Additional beta2-agonist use (parallel studies).

Study or subgroup	Xanthine n/N	ICS n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.11.1 Parallel group					
Meltzer 1992	24/35	16/37		25.28%	2.86[1.09,7.52]
Tinkelman 1993	42/64	45/73		74.72%	1.19[0.59,2.39]
Subtotal (95% CI)	**99**	**110**		**100%**	**1.61[0.92,2.82]**
Total events: 66 (Xanthine), 61 (ICS)					
Heterogeneity: Tau^2=0; Chi^2=2.09, df=1(P=0.15); I^2=52.23%					
Test for overall effect: Z=1.67(P=0.1)					



Analysis 2.12. Comparison 2 Xanthine versus inhaled corticosteroids, Outcome 12 FEV1 % predicted - post bronchodilator use (parallel studies).

Study or subgroup	Xanthine N	Xanthine Mean(SD)	ICS N	ICS Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Meltzer 1992	88	89 (28)	88	93 (28)		27.12%	-4[-12.27,4.27]
Tinkelman 1993	69	92 (15)	76	94 (16)		72.88%	-2[-7.05,3.05]
Total ***	**157**		**164**			**100%**	**-2.54[-6.85,1.77]**



Study or subgroup	Xanthine N	Xanthine Mean(SD)	ICS N	ICS Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=0.16, df=1(P=0.69); I²=0%							
Test for overall effect: Z=1.16(P=0.25)							

Favours ICS -10 -5 0 5 10 Favours xanthine

Analysis 2.13. Comparison 2 Xanthine versus inhaled corticosteroids, Outcome 13 PEF % predicted - daily (parallel studies).

Study or subgroup	Xanthine N	Xanthine Mean(SD)	ICS N	ICS Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Tinkelman 1993	69	92.4 (19.4)	76	97 (20.6)		0%	-4.6[-11.11,1.91]

Favours ICS -100 -50 0 50 100 Favours xanthine

Analysis 2.14. Comparison 2 Xanthine versus inhaled corticosteroids, Outcome 14 Morning PEF % predicted (parallel studies).

Study or subgroup	Xanthine N	Xanthine Mean(SD)	ICS N	ICS Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Tinkelman 1993	69	91.3 (20.6)	76	95.9 (20)		0%	-4.6[-11.22,2.02]

Favours ICS -100 -50 0 50 100 Favours xanthine

Analysis 2.15. Comparison 2 Xanthine versus inhaled corticosteroids, Outcome 15 FEF25-75 (parallel studies).

Study or subgroup	Xanthine N	Xanthine Mean(SD)	ICS N	ICS Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Meltzer 1992	26	65 (66.3)	33	80 (91.9)		0%	-15[-55.41,25.41]

Favours ICS -100 -50 0 50 100 Favours xanthine

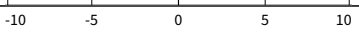
Analysis 2.16. Comparison 2 Xanthine versus inhaled corticosteroids, Outcome 16 Growth rate observed minus predicted (parallel studies).

Study or subgroup	Xanthine N	Xanthine Mean(SD)	ICS N	ICS Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Tinkelman 1993	81	0.4 (2.6)	86	-0.7 (2.4)		1.1[0.34,1.86]

Favours ICS -10 -5 0 5 10 Favours xanthine

Analysis 2.17. Comparison 2 Xanthine versus inhaled corticosteroids, Outcome 17 Total problems after one year (summary score for the Child Behaviour Checklist - parallel studies).

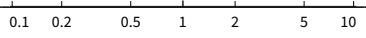
Study or subgroup	Xanthine N	Xanthine Mean(SD)	ICS N	ICS Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Tinkelman 1993	50	52.5 (11.3)	52	53.6 (12.3)		0%	-1.1[-5.68,3.48]



Favours xanthine — Favours ICS

Analysis 2.18. Comparison 2 Xanthine versus inhaled corticosteroids, Outcome 18 Side effects (headache - parallel studies).

Study or subgroup	Xanthine n/N	ICS n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Meltzer 1992	17/39	15/37		33.6%	1.13[0.46,2.82]
Tinkelman 1993	55/108	34/102		66.4%	2.08[1.19,3.63]
Total (95% CI)	**147**	**139**		**100%**	**1.76[1.09,2.83]**
Total events: 72 (Xanthine), 49 (ICS)					
Heterogeneity: Tau^2=0; Chi^2=1.23, df=1(P=0.27); I^2=18.71%					
Test for overall effect: Z=2.33(P=0.02)					



Favours xanthine — Favours ICS

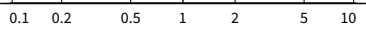
Analysis 2.19. Comparison 2 Xanthine versus inhaled corticosteroids, Outcome 19 Side effects (tremors - parallel studies).

Study or subgroup	Xanthine n/N	ICS n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Meltzer 1992	3/39	6/37		92.59%	0.43[0.1,1.87]
Tinkelman 1993	6/102	0/108		7.41%	14.62[0.81,262.87]
Total (95% CI)	**141**	**145**		**100%**	**1.48[0.53,4.14]**
Total events: 9 (Xanthine), 6 (ICS)					
Heterogeneity: Tau^2=0; Chi^2=5.14, df=1(P=0.02); I^2=80.54%					
Test for overall effect: Z=0.75(P=0.45)					

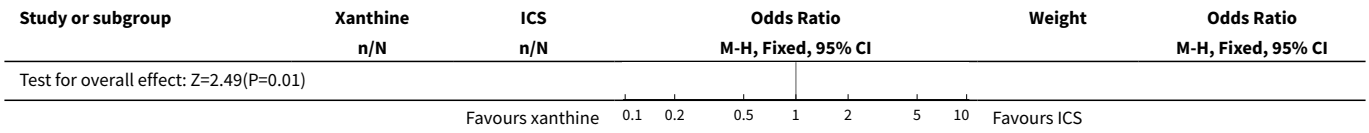
Favours xanthine — Favours ICS

Analysis 2.20. Comparison 2 Xanthine versus inhaled corticosteroids, Outcome 20 Side effects (nausea - parallel studies).

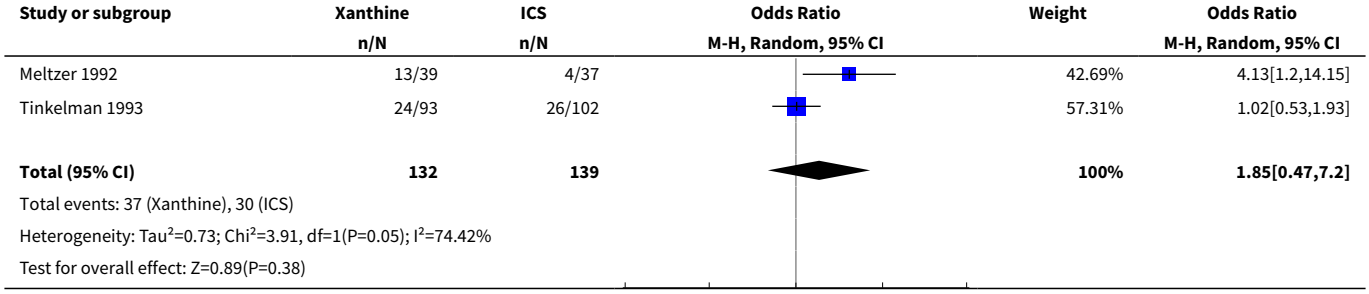
Study or subgroup	Xanthine n/N	ICS n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Meltzer 1992	11/39	7/37		26.92%	1.68[0.57,4.95]
Tinkelman 1993	38/108	21/102		73.08%	2.09[1.12,3.9]
Total (95% CI)	**147**	**139**		**100%**	**1.98[1.16,3.4]**
Total events: 49 (Xanthine), 28 (ICS)					
Heterogeneity: Tau^2=0; Chi^2=0.12, df=1(P=0.73); I^2=0%					



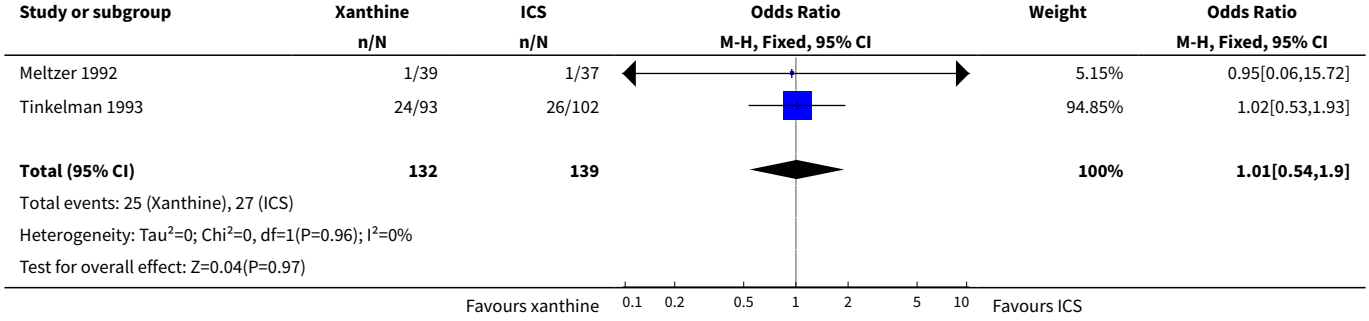
Favours xanthine — Favours ICS



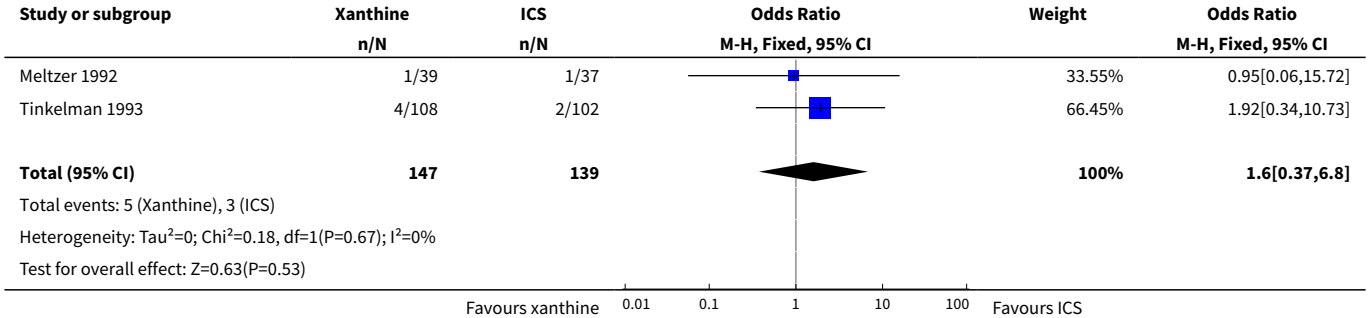
Analysis 2.21. Comparison 2 Xanthine versus inhaled corticosteroids, Outcome 21 Withdrawal from study (parallel studies).



Analysis 2.22. Comparison 2 Xanthine versus inhaled corticosteroids, Outcome 22 Withdrawal due to lack of benefit (parallel studies).

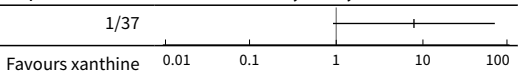


Analysis 2.23. Comparison 2 Xanthine versus inhaled corticosteroids, Outcome 23 Withdrawal from study due to adverse effect (parallel studies).



Analysis 2.24. Comparison 2 Xanthine versus inhaled corticosteroids, Outcome 24 Withdrawal due to exacerbation (parallel studies).

Study or subgroup	Xanthine n/N	ICS n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Meltzer 1992	7/39	1/37		7.88[0.92,67.52]



Comparison 3. Xanthine versus beta2-agonists

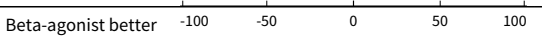
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom free days (crossover studies)	3		% (Fixed, 95% CI)	5.70 [-2.11, 13.51]
2 Symptom free days (day wheeze - crossover studies)	2		% (Fixed, 95% CI)	-4.20 [-16.02, 7.62]
3 Symptom free days (activity - crossover studies)	1		% (Fixed, 95% CI)	Totals not selected
4 Symptom free days (cough - crossover studies)	2		% (Fixed, 95% CI)	3.34 [-10.23, 16.91]
5 Symptom free days (sleep - crossover studies)	2		% (Fixed, 95% CI)	0.22 [-6.33, 6.77]
6 Symptom score (total - crossover studies)	1		Symptoms (Fixed, 95% CI)	Totals not selected
7 Symptom score (day wheeze - crossover studies)	4		SD units (Fixed, 95% CI)	-0.09 [-0.31, 0.14]
8 Symptom score (daytime shortness of breath - crossover studies)	1		Symptoms (Fixed, 95% CI)	Totals not selected
9 Symptom score (daytime chest tightness - crossover studies)	1		Symptoms (Fixed, 95% CI)	Totals not selected
10 Symptom score (activity - crossover studies)	0		Symptoms (Fixed, 95% CI)	Totals not selected
11 Symptom score (cough - crossover studies)	3		SD units (Fixed, 95% CI)	-0.27 [-0.55, -0.00]
12 Symptom score (nighttime - crossover studies)	4		SD units (Fixed, 95% CI)	-0.20 [-0.43, 0.03]
13 Hospitalisation/ER treatment (crossover studies)	3	110	Odds Ratio (M-H, Fixed, 95% CI)	6.00 [1.40, 25.60]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
14 Attacks of asthma (daytime)	1		Attacks/participant (Fixed, 95% CI)	Totals not selected
15 Attacks of asthma (night)	1		Attacks/participant (Fixed, 95% CI)	Totals not selected
16 Number of patients requiring oral steroids	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
17 Rescue medication usage (crossover studies)	2		Puffs/day (Fixed, 95% CI)	-0.38 [-0.93, 0.18]
18 Rescue medication usage (weekly score - crossover studies)	1		Weekly score (Fixed, 95% CI)	Totals not selected
19 FEV1 (crossover studies)	1		Litres (Fixed, 95% CI)	Totals not selected
20 FEV1 (predicted - crossover studies)	1		% (Fixed, 95% CI)	Totals not selected
21 FEV1 (parallel groups/first arm crossover)	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
22 Morning PEF (crossover studies)	2		L/min (Fixed, 95% CI)	18.13 [3.59, 32.68]
23 Evening PEF (crossover studies)	2		L/min (Fixed, 95% CI)	8.66 [1.71, 15.60]
24 PEF (clinic - crossover studies)	1		L/min (Fixed, 95% CI)	Totals not selected
25 PEF (clinic predicted - crossover studies)	1		% (Fixed, 95% CI)	Totals not selected
26 PEF (diurnal variation - crossover studies)	0		% (Fixed, 95% CI)	Totals not selected
27 RV/TLC (crossover studies)	1		% (Fixed, 95% CI)	Totals not selected
28 Side effects (any - crossover studies)	2	62	Odds Ratio (M-H, Fixed, 95% CI)	2.1 [0.38, 11.59]
29 Abdominal pain (crossover studies)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
30 Diarrhea (crossover studies)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
31 Vomiting (crossover studies)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
32 Headache (crossover studies)	2	106	Odds Ratio (M-H, Fixed, 95% CI)	2.74 [1.15, 6.55]
33 Nervousness (crossover studies)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
34 Insomnia (crossover studies)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
35 Tremor (crossover studies)	2	106	Odds Ratio (M-H, Fixed, 95% CI)	0.17 [0.06, 0.50]
36 Palpitations (crossover studies)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
37 Bad taste	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
38 Nausea	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 Xanthine versus beta2-agonists, Outcome 1 Symptom free days (crossover studies).

Study or subgroup	Xanthine N	Beta-agonist N	% (SE)	% IV, Fixed, 95% CI	Weight	% IV, Fixed, 95% CI
Chow 1989	24	24	3.1 (7.316)		29.65%	3.1[-11.24,17.44]
Dusdieker 1982	36	36	15 (6.301)		39.97%	15[2.65,27.35]
Nolan 1982	11	11	-4 (7.227)		30.38%	-4[-18.16,10.16]
Total (95% CI)					**100%**	**5.7[-2.11,13.51]**
Heterogeneity: Tau^2=0; Chi^2=4.11, df=2(P=0.13); I^2=51.29%						
Test for overall effect: Z=1.43(P=0.15)						



Analysis 3.2. Comparison 3 Xanthine versus beta2-agonists, Outcome 2 Symptom free days (day wheeze - crossover studies).

Study or subgroup	Xanthine N	Beta-agonist N	% (SE)	% IV, Fixed, 95% CI	Weight	% IV, Fixed, 95% CI
Chow 1989	24	24	-0.7 (8.53)		50%	-0.7[-17.42,16.02]
Nolan 1982	11	11	-7.7 (8.531)		50%	-7.7[-24.42,9.02]
Total (95% CI)					**100%**	**-4.2[-16.02,7.62]**
Heterogeneity: Tau^2=0; Chi^2=0.34, df=1(P=0.56); I^2=0%						
Test for overall effect: Z=0.7(P=0.49)						

Analysis 3.3. Comparison 3 Xanthine versus beta2-agonists, Outcome 3 Symptom free days (activity - crossover studies).

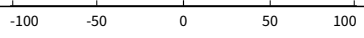
Study or subgroup	Xanthine N	Beta-agonist N	% (SE)	% IV, Fixed, 95% CI	% IV, Fixed, 95% CI
Chow 1989	24	24	-0.5 (6.59)		-0.5[-13.42,12.42]

Analysis 3.4. Comparison 3 Xanthine versus beta2-agonists, Outcome 4 Symptom free days (cough - crossover studies).

Study or subgroup	Xanthine N	Beta-agonist N	% (SE)	% IV, Fixed, 95% CI	Weight	% IV, Fixed, 95% CI
Chow 1989	24	24	7 (8.556)		65.46%	7[-9.77,23.77]
Nolan 1982	11	11	-3.6 (11.78)		34.54%	-3.6[-26.69,19.49]
Total (95% CI)					**100%**	**3.34[-10.23,16.91]**

Heterogeneity: Tau²=0; Chi²=0.53, df=1(P=0.47); I²=0%

Test for overall effect: Z=0.48(P=0.63)

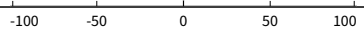


Analysis 3.5. Comparison 3 Xanthine versus beta2-agonists, Outcome 5 Symptom free days (sleep - crossover studies).

Study or subgroup	Xanthine N	Beta-agonist N	% (SE)	% IV, Fixed, 95% CI	Weight	% IV, Fixed, 95% CI
Chow 1989	24	24	6.4 (5.709)		34.27%	6.4[-4.79,17.59]
Nolan 1982	11	11	-3 (4.122)		65.73%	-3[-11.08,5.08]
Total (95% CI)					**100%**	**0.22[-6.33,6.77]**

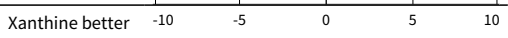
Heterogeneity: Tau²=0; Chi²=1.78, df=1(P=0.18); I²=43.88%

Test for overall effect: Z=0.07(P=0.95)



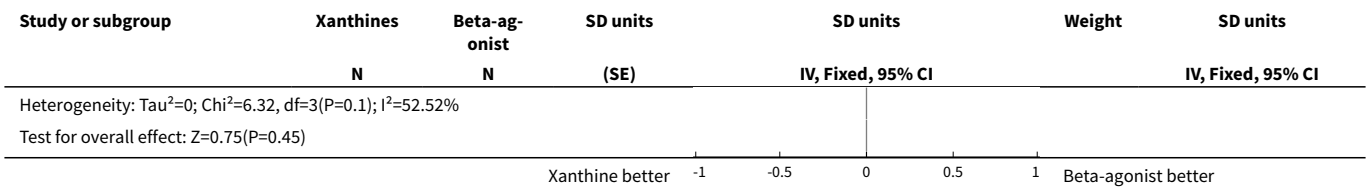
Analysis 3.6. Comparison 3 Xanthine versus beta2-agonists, Outcome 6 Symptom score (total - crossover studies).

Study or subgroup	Xanthine N	Beta-agonist N	Symptoms (SE)	Symptoms IV, Fixed, 95% CI	Symptoms IV, Fixed, 95% CI
Rachelefsky 1980	20	20	-2.1 (1.027)		-2.08[-4.09,-0.07]

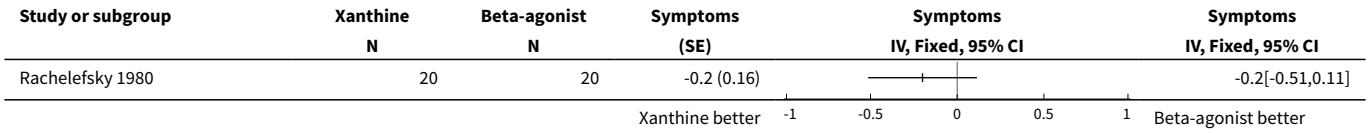


Analysis 3.7. Comparison 3 Xanthine versus beta2-agonists, Outcome 7 Symptom score (day wheeze - crossover studies).

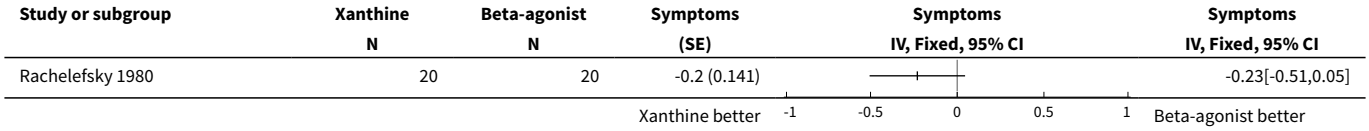
Study or subgroup	Xanthines N	Beta-agonist N	SD units (SE)	SD units IV, Fixed, 95% CI	Weight	SD units IV, Fixed, 95% CI
Chow 1989	24	24	-0 (0.204)		32.01%	-0.02[-0.42,0.38]
Nolan 1982	11	11	0.5 (0.301)		14.7%	0.54[-0.05,1.13]
Rachelefsky 1980	20	20	-0.3 (0.224)		26.64%	-0.35[-0.79,0.09]
Schuller 1982	20	20	-0.2 (0.224)		26.64%	-0.24[-0.68,0.19]
Total (95% CI)					**100%**	**-0.09[-0.31,0.14]**



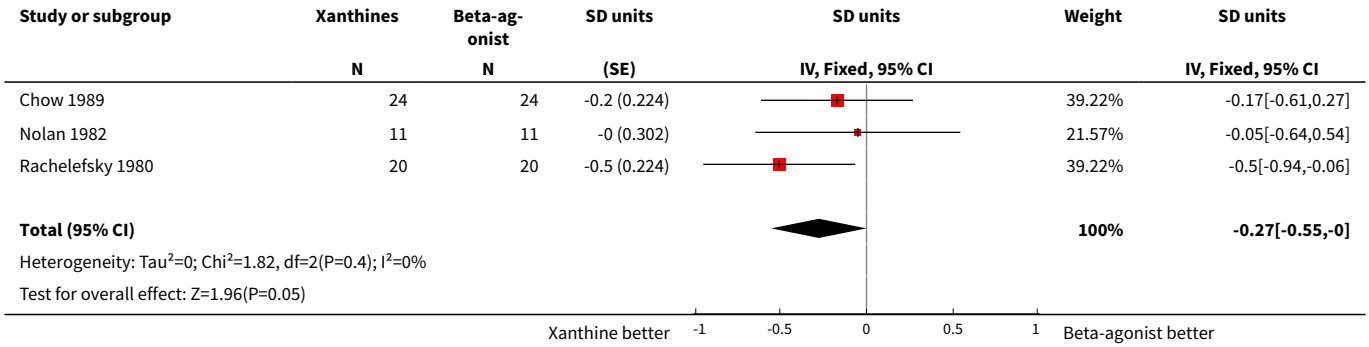
Analysis 3.8. Comparison 3 Xanthine versus beta2-agonists, Outcome 8 Symptom score (daytime shortness of breath - crossover studies).



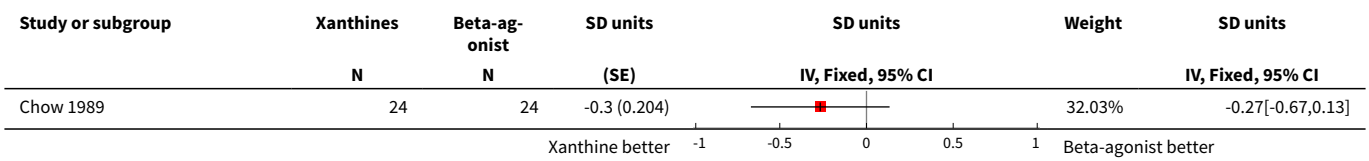
Analysis 3.9. Comparison 3 Xanthine versus beta2-agonists, Outcome 9 Symptom score (daytime chest tightness - crossover studies).



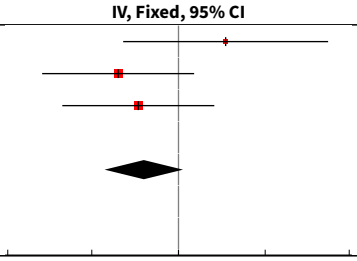
Analysis 3.11. Comparison 3 Xanthine versus beta2-agonists, Outcome 11 Symptom score (cough - crossover studies).



Analysis 3.12. Comparison 3 Xanthine versus beta2-agonists, Outcome 12 Symptom score (nighttime - crossover studies).

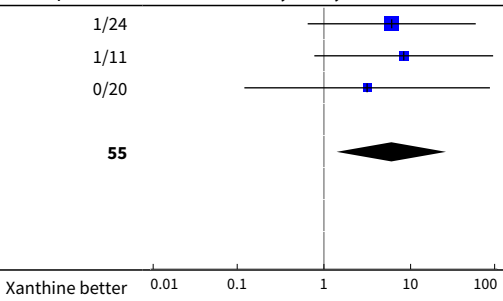


Study or subgroup	Xanthines	Beta-agonist	SD units	SD units	Weight	SD units
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
Nolan 1982	11	11	0.3 (0.302)		14.66%	0.27[-0.32,0.86]
Rachelefsky 1980	20	20	-0.3 (0.224)		26.66%	-0.35[-0.79,0.09]
Schuller 1982	20	20	-0.2 (0.224)		26.66%	-0.23[-0.67,0.21]
Total (95% CI)					**100%**	**-0.2[-0.43,0.03]**
Heterogeneity: Tau²=0; Chi²=3.02, df=3(P=0.39); I²=0.53%						
Test for overall effect: Z=1.73(P=0.08)						



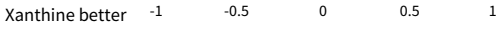
Analysis 3.13. Comparison 3 Xanthine versus beta2-agonists, Outcome 13 Hospitalisation/ER treatment (crossover studies).

Study or subgroup	Xanthine	Beta-agonist	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Chow 1989	5/24	1/24		43.95%	6.05[0.65,56.37]
Nolan 1982	5/11	1/11		30.28%	8.33[0.78,89.47]
Schuller 1982	1/20	0/20		25.77%	3.15[0.12,82.16]
Total (95% CI)	**55**	**55**		**100%**	**6[1.4,25.6]**
Total events: 11 (Xanthine), 2 (Beta-agonist)					
Heterogeneity: Tau²=0; Chi²=0.22, df=2(P=0.89); I²=0%					
Test for overall effect: Z=2.42(P=0.02)					



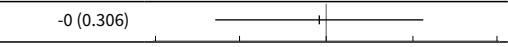
Analysis 3.14. Comparison 3 Xanthine versus beta2-agonists, Outcome 14 Attacks of asthma (daytime).

Study or subgroup	Xanthine	Beta-agonist	Attacks/participant	Attacks/participant	Attacks/participant
	N	N	(SE)	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Rachelefsky 1980	20	20	-0.1 (0.059)		-0.13[-0.25,-0.01]



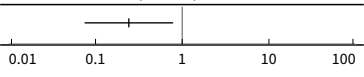
Analysis 3.15. Comparison 3 Xanthine versus beta2-agonists, Outcome 15 Attacks of asthma (night).

Study or subgroup	Xanthine	Beta-agonist	Attacks/participant	Attacks/participant	Attacks/participant
	N	N	(SE)	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Rachelefsky 1980	20	20	-0 (0.306)		-0.04[-0.64,0.56]



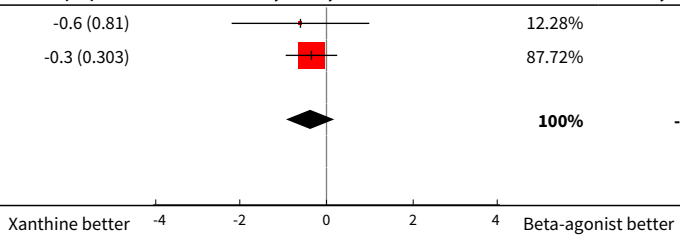
Analysis 3.16. Comparison 3 Xanthine versus beta2-agonists, Outcome 16 Number of patients requiring oral steroids.

Study or subgroup	Xanthine n/N	Beta-agonist n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Dusdieker 1982	5/33	14/33		0.24[0.07,0.79]



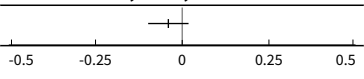
Analysis 3.17. Comparison 3 Xanthine versus beta2-agonists, Outcome 17 Rescue medication usage (crossover studies).

Study or subgroup	Xanthine N	Beta-agonist N	Puffs/day (SE)	Puffs/day IV, Fixed, 95% CI	Weight	Puffs/day IV, Fixed, 95% CI
Chow 1989	24	24	-0.6 (0.81)		12.28%	-0.6[-2.19,0.99]
Rachelefsky 1980	20	20	-0.3 (0.303)		87.72%	-0.35[-0.94,0.25]
Total (95% CI)					**100%**	**-0.38[-0.93,0.18]**
Heterogeneity: Tau^2=0; Chi^2=0.09, df=1(P=0.77); I^2=0%						
Test for overall effect: Z=1.33(P=0.18)						



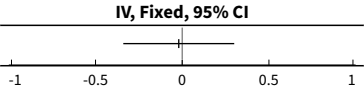
Analysis 3.18. Comparison 3 Xanthine versus beta2-agonists, Outcome 18 Rescue medication usage (weekly score - crossover studies).

Study or subgroup	Xanthine N	Beta-agonist N	Weekly score (SE)	Weekly score IV, Fixed, 95% CI	Weekly score IV, Fixed, 95% CI
Nolan 1982	11	11	-0 (0.03)		-0.04[-0.1,0.02]



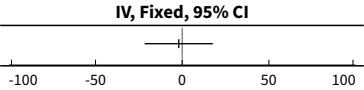
Analysis 3.19. Comparison 3 Xanthine versus beta2-agonists, Outcome 19 FEV1 (crossover studies).

Study or subgroup	Xanthines N	Beta-agonist N	Litres (SE)	Litres IV, Fixed, 95% CI	Litres IV, Fixed, 95% CI
Chow 1989	24	24	-0 (0.163)		-0.02[-0.34,0.3]



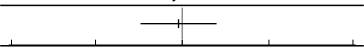
Analysis 3.20. Comparison 3 Xanthine versus beta2-agonists, Outcome 20 FEV1 (predicted - crossover studies).

Study or subgroup	Xanthines N	Beta-agonist N	% (SE)	% IV, Fixed, 95% CI	% IV, Fixed, 95% CI
Dusdieker 1982	15	15	-2 (10.04)		-2[-21.68,17.68]



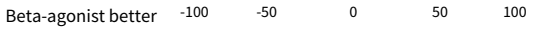
Analysis 3.21. Comparison 3 Xanthine versus beta2-agonists, Outcome 21 FEV1 (parallel groups/first arm crossover).

Study or subgroup	Xanthine N	Xanthine Mean(SD)	Beta-agonist N	Beta-agonist Mean(SD)	Std. Mean Difference Fixed, 95% CI	Std. Mean Difference Fixed, 95% CI
Rachelefsky 1980	10	56 (15)	10	58 (28)		-0.09[-0.96,0.79]



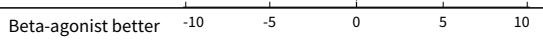
Analysis 3.22. Comparison 3 Xanthine versus beta2-agonists, Outcome 22 Morning PEF (crossover studies).

Study or subgroup	Xanthine N	Beta-agonist N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
Chow 1989	24	24	10 (17.17)		18.68%	10[-23.65,43.65]
Rachelefsky 1980	20	20	20 (8.23)		81.32%	20[3.87,36.13]
Total (95% CI)					**100%**	**18.13[3.59,32.68]**
Heterogeneity: Tau²=0; Chi²=0.28, df=1(P=0.6); I²=0%						
Test for overall effect: Z=2.44(P=0.01)						



Analysis 3.23. Comparison 3 Xanthine versus beta2-agonists, Outcome 23 Evening PEF (crossover studies).

Study or subgroup	Xanthine N	Beta-agonist N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
Chow 1989	24	24	5 (12.07)		8.61%	5[-18.66,28.66]
Rachelefsky 1980	20	20	9 (3.705)		91.39%	9[1.74,16.26]
Total (95% CI)					**100%**	**8.66[1.71,15.6]**
Heterogeneity: Tau²=0; Chi²=0.1, df=1(P=0.75); I²=0%						
Test for overall effect: Z=2.44(P=0.01)						

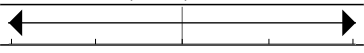


Analysis 3.24. Comparison 3 Xanthine versus beta2-agonists, Outcome 24 PEF (clinic - crossover studies).

Study or subgroup	Xanthines N	Beta-agonist N	L/min (SE)	L/min IV, Fixed, 95% CI	L/min IV, Fixed, 95% CI
Chow 1989	24	24	0 (19.81)		0[-38.83,38.83]

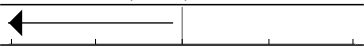
Analysis 3.25. Comparison 3 Xanthine versus beta2-agonists, Outcome 25 PEF (clinic predicted - crossover studies).

Study or subgroup	Xanthines N	Beta-agonist N	% (SE)	% IV, Fixed, 95% CI	% IV, Fixed, 95% CI
Dusdieker 1982	15	15	8 (5.658)		8[-3.09,19.09]



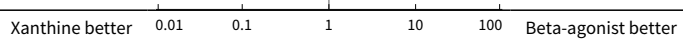
Analysis 3.27. Comparison 3 Xanthine versus beta2-agonists, Outcome 27 RV/TLC (crossover studies).

Study or subgroup	Xanthine N	Beta-agonist N	% (SE)	% IV, Fixed, 95% CI	% IV, Fixed, 95% CI
Dusdieker 1982	33	33	-6.6 (3.26)		-6.6[-12.99,-0.21]



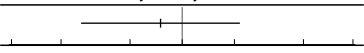
Analysis 3.28. Comparison 3 Xanthine versus beta2-agonists, Outcome 28 Side effects (any - crossover studies).

Study or subgroup	Xanthine n/N	Beta-agonist n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Nolan 1982	7/11	5/11		100%	2.1[0.38,11.59]
Schuller 1982	0/20	0/20			Not estimable
Total (95% CI)	**31**	**31**		**100%**	**2.1[0.38,11.59]**
Total events: 7 (Xanthine), 5 (Beta-agonist)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.85(P=0.39)					



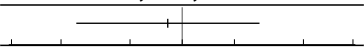
Analysis 3.29. Comparison 3 Xanthine versus beta2-agonists, Outcome 29 Abdominal pain (crossover studies).

Study or subgroup	Xanthine n/N	Beta-agonists n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Dusdieker 1982	9/33	11/33		0.75[0.26,2.15]

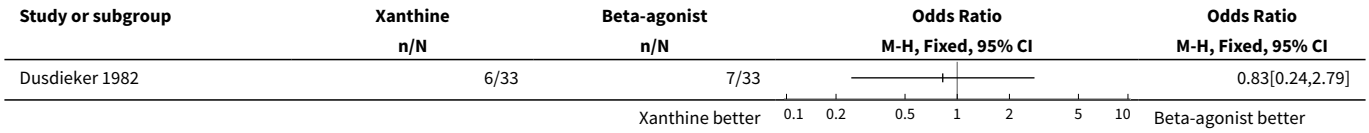


Analysis 3.30. Comparison 3 Xanthine versus beta2-agonists, Outcome 30 Diarrhea (crossover studies).

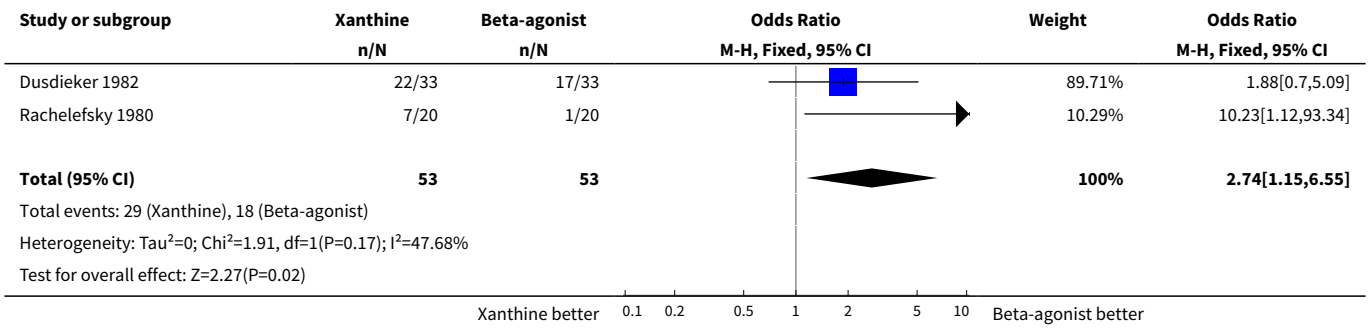
Study or subgroup	Xanthine n/N	Beta-agonists n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Dusdieker 1982	6/33	7/33		0.83[0.24,2.79]



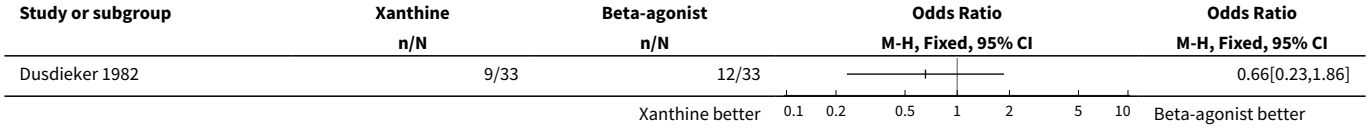
Analysis 3.31. Comparison 3 Xanthine versus beta2-agonists, Outcome 31 Vomiting (crossover studies).



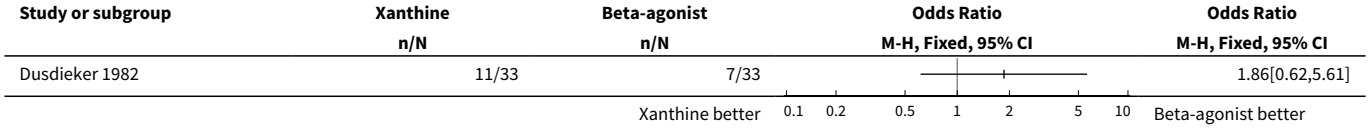
Analysis 3.32. Comparison 3 Xanthine versus beta2-agonists, Outcome 32 Headache (crossover studies).



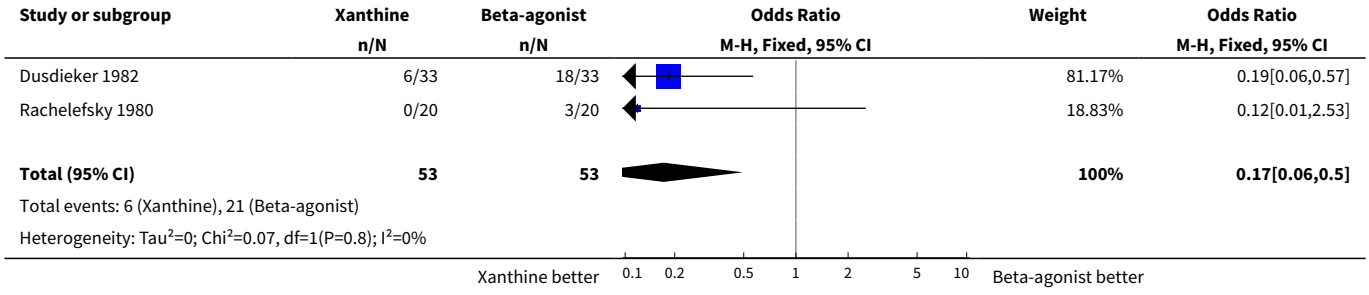
Analysis 3.33. Comparison 3 Xanthine versus beta2-agonists, Outcome 33 Nervousness (crossover studies).

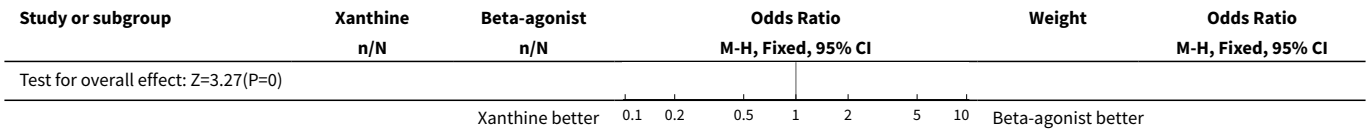


Analysis 3.34. Comparison 3 Xanthine versus beta2-agonists, Outcome 34 Insomnia (crossover studies).

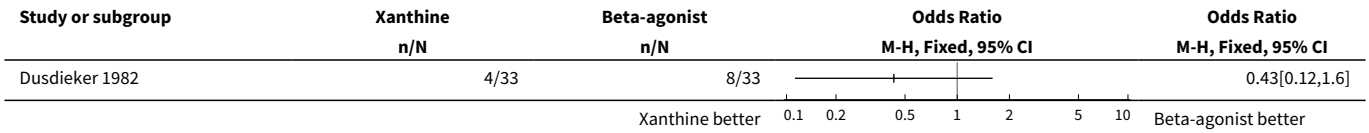


Analysis 3.35. Comparison 3 Xanthine versus beta2-agonists, Outcome 35 Tremor (crossover studies).

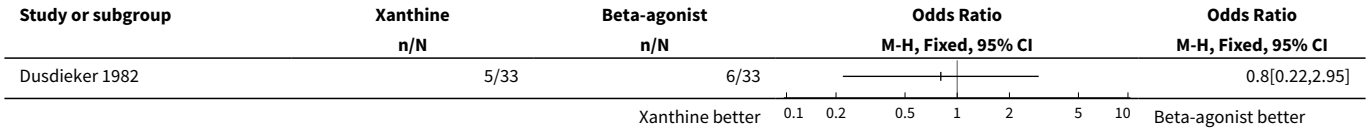




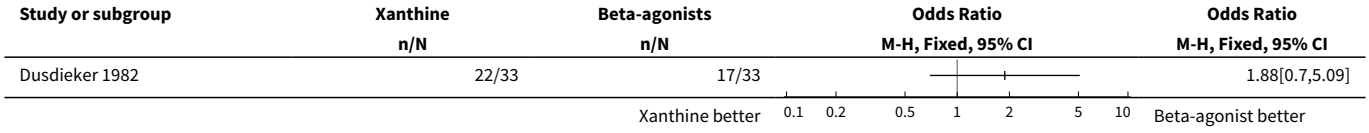
Analysis 3.36. Comparison 3 Xanthine versus beta2-agonists, Outcome 36 Palpitations (crossover studies).



Analysis 3.37. Comparison 3 Xanthine versus beta2-agonists, Outcome 37 Bad taste.



Analysis 3.38. Comparison 3 Xanthine versus beta2-agonists, Outcome 38 Nausea.



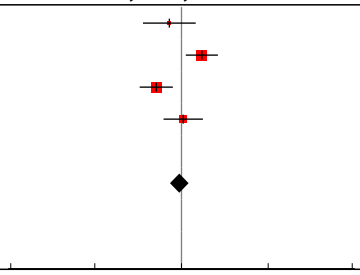
Comparison 4. Xanthine versus sodium cromoglycate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom free days (crossover studies)	4		% (Fixed, 95% CI)	-1.27 [-6.64, 4.10]
2 Symptom score (crossover studies)	2		SD units (Fixed, 95% CI)	0.42 [0.12, 0.71]
3 Improvement in asthma severity (parallel groups)	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4 Hospitalisation (crossover studies)	2	84	Odds Ratio (M-H, Fixed, 95% CI)	1.71 [0.22, 13.46]
5 Severe attacks of asthma	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6 Number of patients requiring steroids (crossover studies)	2	88	Odds Ratio (M-H, Fixed, 95% CI)	2.08 [0.18, 24.31]

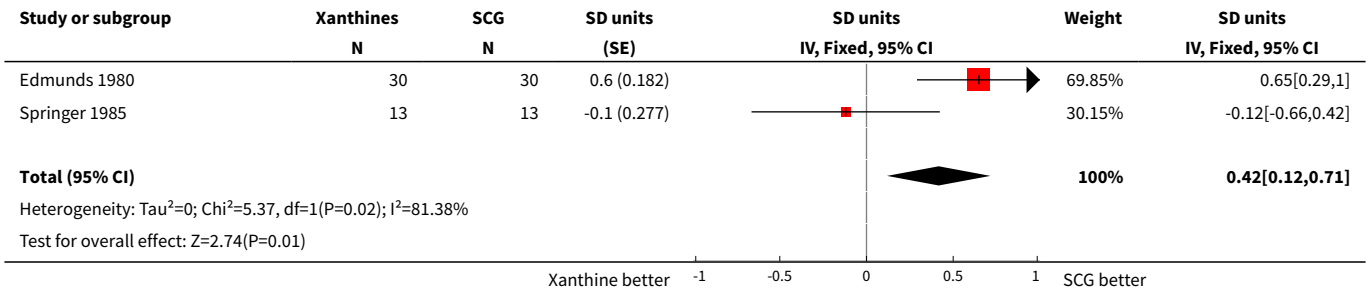
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Rescue medication usage (crossover studies)	4		Puffs/day (Fixed, 95% CI)	-0.06 [-0.15, 0.04]
8 PEF- daily (crossover studies)	1		% predicted (Fixed, 95% CI)	Totals not selected
9 Morning PEF (predicted - crossover studies)	0		% (Fixed, 95% CI)	Totals not selected
10 Evening PEF (predicted - crossover studies)	0		% (Fixed, 95% CI)	Totals not selected
11 Proportion of days when PEF < 50% predicted	0		% (Fixed, 95% CI)	Totals not selected
12 Patients with reduction in bronchial reactivity	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
13 Side effects (gastro-intestinal - crossover studies)	2	108	Odds Ratio (M-H, Fixed, 95% CI)	6.28 [1.46, 27.08]
14 Side-effects (insomnia - crossover studies)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
15 Side effects (restlessness - crossover studies)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
16 Withdrawal from trial (parallel group/ first arm data)	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Analysis 4.1. Comparison 4 Xanthine versus sodium cromoglycate, Outcome 1 Symptom free days (crossover studies).

Study or subgroup	Xanthine N	SCG N	% (SE)	% IV, Fixed, 95% CI	Weight	% IV, Fixed, 95% CI
Edmunds 1980	30	30	-7 (7.76)		12.45%	-7[-22.21,8.21]
Hambleton 1977	28	28	11.8 (4.72)		33.66%	11.75[2.5,21]
Newth 1982	26	26	-14.5 (4.88)		31.49%	-14.54[-24.1,-4.97]
Springer 1985	13	13	1 (5.787)		22.4%	1[-10.34,12.34]
Total (95% CI)					**100%**	**-1.27[-6.64,4.1]**
Heterogeneity: Tau²=0; Chi²=15.7, df=3(P=0); I²=80.89%						
Test for overall effect: Z=0.46(P=0.64)						

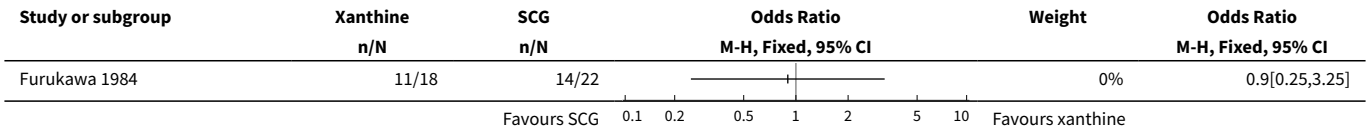


Analysis 4.2. Comparison 4 Xanthine versus sodium cromoglycate, Outcome 2 Symptom score (crossover studies).



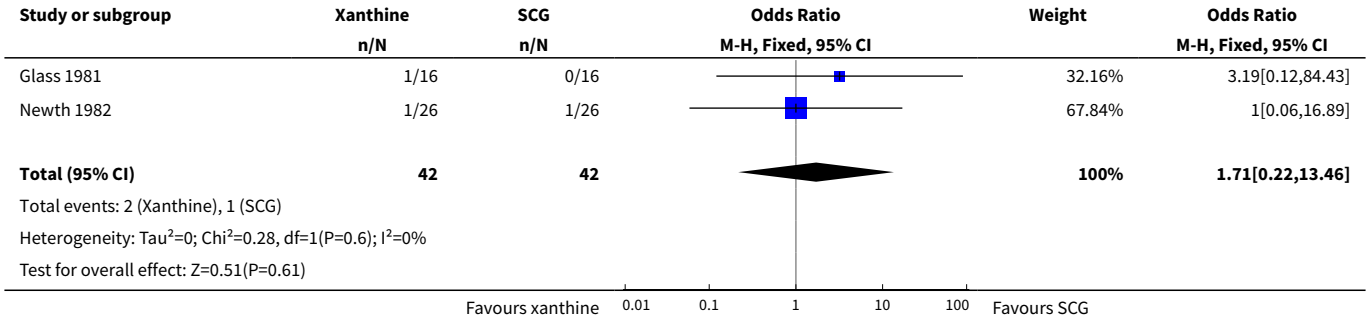
Study or subgroup	Xanthines N	SCG N	SD units (SE)	SD units IV, Fixed, 95% CI	Weight	SD units IV, Fixed, 95% CI
Edmunds 1980	30	30	0.6 (0.182)		69.85%	0.65[0.29,1]
Springer 1985	13	13	-0.1 (0.277)		30.15%	-0.12[-0.66,0.42]
Total (95% CI)					**100%**	**0.42[0.12,0.71]**
Heterogeneity: Tau²=0; Chi²=5.37, df=1(P=0.02); I²=81.38%						
Test for overall effect: Z=2.74(P=0.01)						

Analysis 4.3. Comparison 4 Xanthine versus sodium cromoglycate, Outcome 3 Improvement in asthma severity (parallel groups).



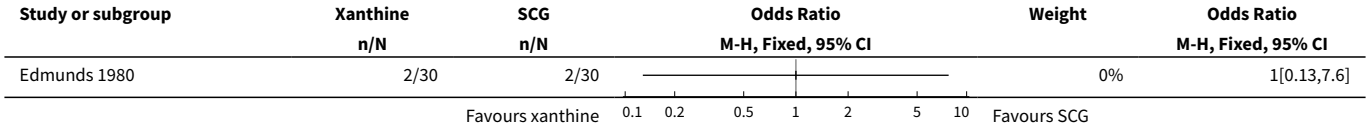
Study or subgroup	Xanthine n/N	SCG n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Furukawa 1984	11/18	14/22		0%	0.9[0.25,3.25]

Analysis 4.4. Comparison 4 Xanthine versus sodium cromoglycate, Outcome 4 Hospitalisation (crossover studies).



Study or subgroup	Xanthine n/N	SCG n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Glass 1981	1/16	0/16		32.16%	3.19[0.12,84.43]
Newth 1982	1/26	1/26		67.84%	1[0.06,16.89]
Total (95% CI)	**42**	**42**		**100%**	**1.71[0.22,13.46]**
Total events: 2 (Xanthine), 1 (SCG)					
Heterogeneity: Tau²=0; Chi²=0.28, df=1(P=0.6); I²=0%					
Test for overall effect: Z=0.51(P=0.61)					

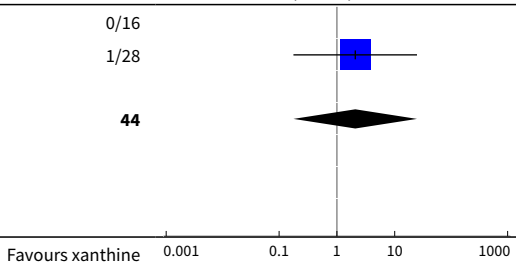
Analysis 4.5. Comparison 4 Xanthine versus sodium cromoglycate, Outcome 5 Severe attacks of asthma.



Study or subgroup	Xanthine n/N	SCG n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Edmunds 1980	2/30	2/30		0%	1[0.13,7.6]

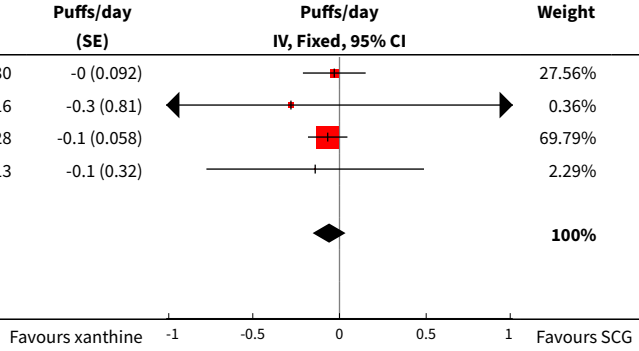
Analysis 4.6. Comparison 4 Xanthine versus sodium cromoglycate, Outcome 6 Number of patients requiring steroids (crossover studies).

Study or subgroup	Xanthine n/N	SCG n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Glass 1981	0/16	0/16			Not estimable
Hambleton 1977	2/28	1/28		100%	2.08[0.18,24.31]
Total (95% CI)	**44**	**44**		**100%**	**2.08[0.18,24.31]**
Total events: 2 (Xanthine), 1 (SCG)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.58(P=0.56)					



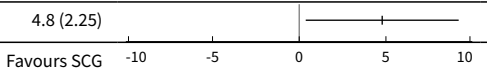
Analysis 4.7. Comparison 4 Xanthine versus sodium cromoglycate, Outcome 7 Rescue medication usage (crossover studies).

Study or subgroup	Xanthine N	SCG N	Puffs/day (SE)	Puffs/day IV, Fixed, 95% CI	Weight	Puffs/day IV, Fixed, 95% CI
Edmunds 1980	30	30	-0 (0.092)		27.56%	-0.03[-0.21,0.15]
Glass 1981	16	16	-0.3 (0.81)		0.36%	-0.28[-1.87,1.31]
Hambleton 1977	28	28	-0.1 (0.058)		69.79%	-0.07[-0.18,0.05]
Springer 1985	13	13	-0.1 (0.32)		2.29%	-0.14[-0.77,0.49]
Total (95% CI)					**100%**	**-0.06[-0.15,0.04]**
Heterogeneity: Tau²=0; Chi²=0.26, df=3(P=0.97); I²=0%						
Test for overall effect: Z=1.24(P=0.22)						



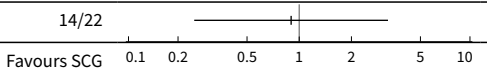
Analysis 4.8. Comparison 4 Xanthine versus sodium cromoglycate, Outcome 8 PEF- daily (crossover studies).

Study or subgroup	Xanthine N	SCG N	% predicted (SE)	% predicted IV, Fixed, 95% CI	% predicted IV, Fixed, 95% CI
Hambleton 1977	28	28	4.8 (2.25)		4.79[0.38,9.19]

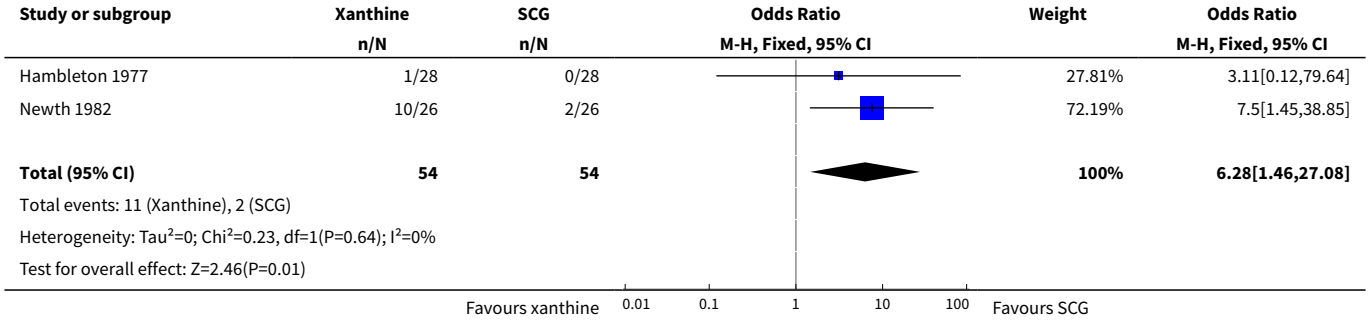


Analysis 4.12. Comparison 4 Xanthine versus sodium cromoglycate, Outcome 12 Patients with reduction in bronchial reactivity.

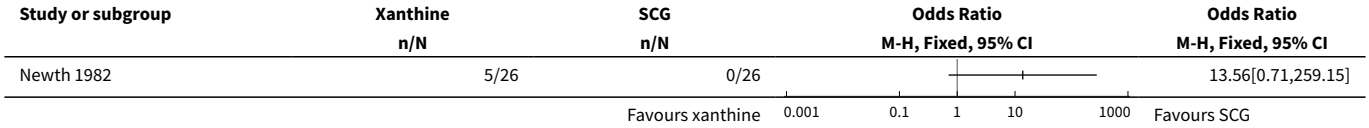
Study or subgroup	Xanthine n/N	SCG n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Furukawa 1984	11/18	14/22		0.9[0.25,3.25]



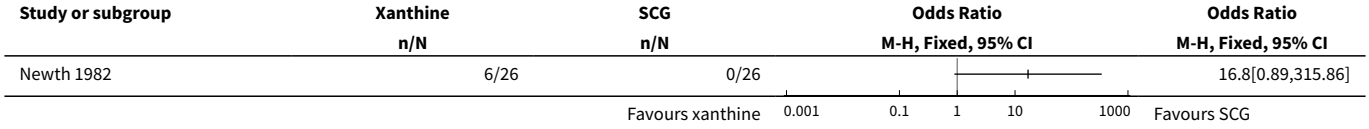
Analysis 4.13. Comparison 4 Xanthine versus sodium cromoglycate, Outcome 13 Side effects (gastro-intestinal - crossover studies).



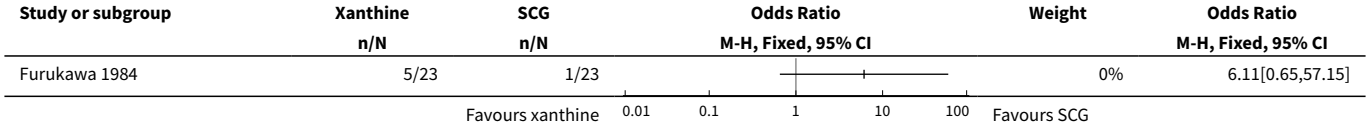
Analysis 4.14. Comparison 4 Xanthine versus sodium cromoglycate, Outcome 14 Side-effects (insomnia - crossover studies).



Analysis 4.15. Comparison 4 Xanthine versus sodium cromoglycate, Outcome 15 Side effects (restlessness - crossover studies).



Analysis 4.16. Comparison 4 Xanthine versus sodium cromoglycate, Outcome 16 Withdrawal from trial (parallel group/first arm data).



Comparison 5. Xanthine versus ketotifen

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Proportion days symptom score low	0		% (Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 PEF	0		% predicted (Fixed, 95% CI)	Totals not selected
3 Days when no salbutamol given	0		% (Fixed, 95% CI)	Totals not selected
4 Days when no additional prednisolone given	0		% (Fixed, 95% CI)	Totals not selected
5 Days when hospital admission necessary	0		% (Fixed, 95% CI)	Totals not selected

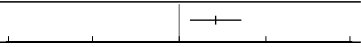
Comparison 6. Xanthine + inhaled corticosteroids versus placebo + inhaled corticosteroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom free days (crossover studies)	1		% (Fixed, 95% CI)	Totals not selected
2 Symptom score (crossover studies)	1		Symptoms (Fixed, 95% CI)	Totals not selected
3 Nocturnal symptom score (parallel groups)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Daytime symptom score (parallel groups)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Morning PEF (predicted - crossover studies)	0		% (Fixed, 95% CI)	Totals not selected
6 Evening PEF (predicted - crossover studies)	0		% (Fixed, 95% CI)	Totals not selected
7 Clinic PEF (pre-BD predicted - crossover studies)	0		% (Fixed, 95% CI)	Totals not selected
8 Clinic PEF (post-BD predicted - crossover studies)	0		% predicted (Fixed, 95% CI)	Totals not selected
9 Clinic PEF (unclear post/pre BD - parallel groups)	1		L/min (Fixed, 95% CI)	Totals not selected
10 FEV1 (pre BD - crossover studies)	0		% predicted (Fixed, 95% CI)	Totals not selected
11 FEV1 (post-BD - crossover studies)	0		% predicted (Fixed, 95% CI)	Totals not selected
12 FVC (pre-BD - crossover studies)	0		% predicted (Fixed, 95% CI)	Totals not selected
13 FVC (post-BD - crossover studies)	0		% predicted (Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14 FEF25-75 (pre BD - crossover studies)	0		% predicted (Fixed, 95% CI)	Totals not selected
15 FEF25-75 (post-BD - crossover studies)	0		% predicted (Fixed, 95% CI)	Totals not selected
16 Residual volume (pre-BD - crossover studies)	0		% predicted (Fixed, 95% CI)	Totals not selected
17 Requirement for prednisone (crossover studies)	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
18 Beta-agonist use (crossover studies)	2		Puffs/day (Fixed, 95% CI)	Totals not selected
19 Beta-agonist use (parallel groups)	1		Puffs/day (Fixed, 95% CI)	Totals not selected
20 Oral steroid consumption (crossover studies)	1		Mg/day (Fixed, 95% CI)	Totals not selected
21 Withdrawals (parallel groups)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
22 Withdrawals due to adverse events (parallel groups)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

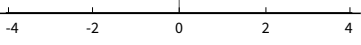
Analysis 6.1. Comparison 6 Xanthine + inhaled corticosteroids versus placebo + inhaled corticosteroids, Outcome 1 Symptom free days (crossover studies).

Study or subgroup	Xanthine + ICS N	Placebo + ICS N	% (SE)	% IV, Fixed, 95% CI	% IV, Fixed, 95% CI
Nassif 1981	22	22	21 (7.56)		21[6.18,35.82]



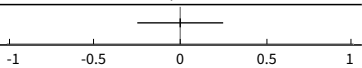
Analysis 6.2. Comparison 6 Xanthine + inhaled corticosteroids versus placebo + inhaled corticosteroids, Outcome 2 Symptom score (crossover studies).

Study or subgroup	Xanthine N	Placebo N	Symptoms (SE)	Symptoms IV, Fixed, 95% CI	Symptoms IV, Fixed, 95% CI
Brenner 1988	5	5	-1.5 (0.13)		-1.48[-1.73,-1.23]



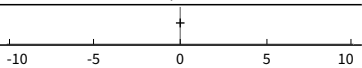
Analysis 6.3. Comparison 6 Xanthine + inhaled corticosteroids versus placebo + inhaled corticosteroids, Outcome 3 Nocturnal symptom score (parallel groups).

Study or subgroup	Xanthine + ICS N	Xanthine + ICS Mean(SD)	Placebo + ICS N	Placebo + ICS Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Süssmuth 2003	15	0.2 (0.4)	17	0.2 (0.3)		0[-0.25,0.25]



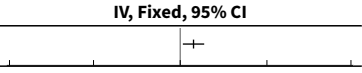
Analysis 6.4. Comparison 6 Xanthine + inhaled corticosteroids versus placebo + inhaled corticosteroids, Outcome 4 Daytime symptom score (parallel groups).

Study or subgroup	Xanthine + ICS N	Xanthine + ICS Mean(SD)	Placebo + ICS N	Placebo + ICS Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Süssmuth 2003	15	0.3 (0.4)	17	0.3 (0.3)		0[-0.25,0.25]



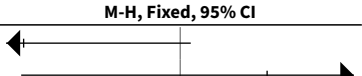
Analysis 6.9. Comparison 6 Xanthine + inhaled corticosteroids versus placebo + inhaled corticosteroids, Outcome 9 Clinic PEF (unclear post/pre BD - parallel groups).

Study or subgroup	Xanthine + ICS N	Placebo + ICS N	L/min (SE)	L/min IV, Fixed, 95% CI	L/min IV, Fixed, 95% CI
Süssmuth 2003	18	18	7.7 (3.14)		7.67[1.52,13.82]



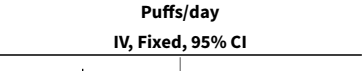
Analysis 6.17. Comparison 6 Xanthine + inhaled corticosteroids versus placebo + inhaled corticosteroids, Outcome 17 Requirement for prednisone (crossover studies).

Study or subgroup	Xanth + ICS n/N	Pla + ICS n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Nassif 1981	1/21	6/21		0.13[0.01,1.15]
Süssmuth 2003	1/18	0/18		3.17[0.12,83.17]



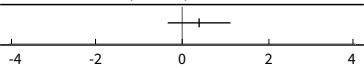
Analysis 6.18. Comparison 6 Xanthine + inhaled corticosteroids versus placebo + inhaled corticosteroids, Outcome 18 Beta-agonist use (crossover studies).

Study or subgroup	Xanthine + ICS N	Placebo + ICS N	Puffs/day (SE)	Puffs/day IV, Fixed, 95% CI	Puffs/day IV, Fixed, 95% CI
Brenner 1988	5	5	-2.2 (0.73)		-2.25[-3.68,-0.82]
Nassif 1981	21	21	-0.5 (0.18)		-0.5[-0.85,-0.15]



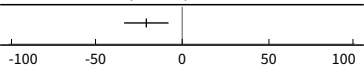
Analysis 6.19. Comparison 6 Xanthine + inhaled corticosteroids versus placebo + inhaled corticosteroids, Outcome 19 Beta-agonist use (parallel groups).

Study or subgroup	Xanthine + ICS N	Placebo + ICS N	Puffs/day (SE)	Puffs/day IV, Fixed, 95% CI	Puffs/day IV, Fixed, 95% CI
Süssmuth 2003	16	17	0.4 (0.37)		0.39[-0.34,1.12]



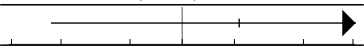
Analysis 6.20. Comparison 6 Xanthine + inhaled corticosteroids versus placebo + inhaled corticosteroids, Outcome 20 Oral steroid consumption (crossover studies).

Study or subgroup	Xanthine + ICS N	Pla + ICS N	Mg/day (SE)	Mg/day IV, Fixed, 95% CI	Mg/day IV, Fixed, 95% CI
Brenner 1988	5	5	-20.7 (6.53)		-20.7[-33.5,-7.9]



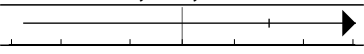
Analysis 6.21. Comparison 6 Xanthine + inhaled corticosteroids versus placebo + inhaled corticosteroids, Outcome 21 Withdrawals (parallel groups).

Study or subgroup	Xanthine + ICS n/N	Placebo + ICS n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Süssmuth 2003	2/18	1/18		2.13[0.18,25.78]



Analysis 6.22. Comparison 6 Xanthine + inhaled corticosteroids versus placebo + inhaled corticosteroids, Outcome 22 Withdrawals due to adverse events (parallel groups).

Study or subgroup	Xanthine + ICS n/N	Placebo + ICS n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Süssmuth 2003	1/18	0/18		3.17[0.12,83.17]



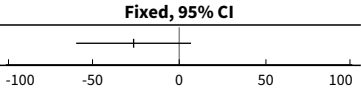
Comparison 7. Xanthine + inhaled corticosteroids versus antileukotriene + inhaled corticosteroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Morning PEF (parallel groups)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Evening PEF (parallel groups)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Rescue medication use (parallel group)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Adverse events (parallel groups)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Headache (parallel groups)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Nausea (parallel groups)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Worsening asthma (parallel groups)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

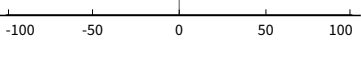
Analysis 7.1. Comparison 7 Xanthine + inhaled corticosteroids versus antileukotriene + inhaled corticosteroids, Outcome 1 Morning PEF (parallel groups).

Study or subgroup	Xanthine + ICS		Antileukotriene + ICS		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Kondo 2006	36	269.3 (71.4)	39	295.6 (74.9)		-26.3[-59.41,6.81]



Analysis 7.2. Comparison 7 Xanthine + inhaled corticosteroids versus antileukotriene + inhaled corticosteroids, Outcome 2 Evening PEF (parallel groups).

Study or subgroup	Xanthine + ICS		Antileukotriene + ICS		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Kondo 2006	36	279.2 (68.4)	39	302.5 (74.9)		-23.3[-55.73,9.13]

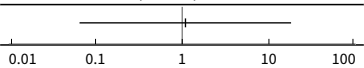


Analysis 7.3. Comparison 7 Xanthine + inhaled corticosteroids versus antileukotriene + inhaled corticosteroids, Outcome 3 Rescue medication use (parallel group).

Study or subgroup	Xanthine + ICS		Antileukotriene + ICS		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Kondo 2006	20	0.7 (1.2)	26	0.6 (0.9)		0.06[-0.57,0.69]

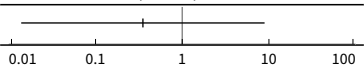
Analysis 7.4. Comparison 7 Xanthine + inhaled corticosteroids versus antileukotriene + inhaled corticosteroids, Outcome 4 Adverse events (parallel groups).

Study or subgroup	Xanthine + ICS n/N	Antileukotriene + ICS n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Kondo 2006	1/36	1/39		1.09[0.07,18.03]



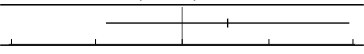
Analysis 7.5. Comparison 7 Xanthine + inhaled corticosteroids versus antileukotriene + inhaled corticosteroids, Outcome 5 Headache (parallel groups).

Study or subgroup	Xanthine + ICS n/N	Antileukotriene + ICS n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Kondo 2006	0/36	1/39		0.35[0.01,8.91]



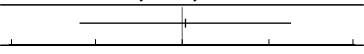
Analysis 7.6. Comparison 7 Xanthine + inhaled corticosteroids versus antileukotriene + inhaled corticosteroids, Outcome 6 Nausea (parallel groups).

Study or subgroup	Xanthine + ICS n/N	Antileukotriene + ICS n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Kondo 2006	1/36	0/39		3.34[0.13,84.6]



Analysis 7.7. Comparison 7 Xanthine + inhaled corticosteroids versus antileukotriene + inhaled corticosteroids, Outcome 7 Worsening asthma (parallel groups).

Study or subgroup	Xanthine + ICS n/N	Antileukotriene + ICS n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Kondo 2006	1/36	1/39		1.09[0.07,18.03]



Comparison 8. SMD comparisons

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total symptom score (SMD) - PLA	3		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Parallel group	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Crossover group	3	126	Std. Mean Difference (IV, Fixed, 95% CI)	-0.40 [-0.82, 0.02]
2 Day symptom score (SMD) - PLA	7		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only

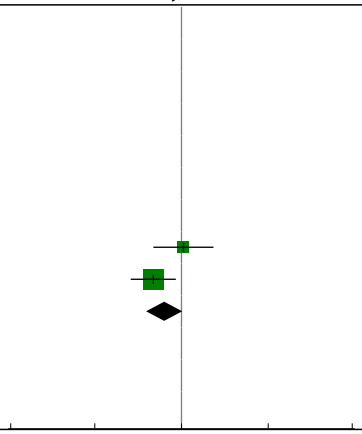
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Parallel group	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Crossover group	7	244	Std. Mean Difference (IV, Fixed, 95% CI)	-0.40 [-0.68, -0.12]
3 Symptom score (day symptoms, estimated SDs) - PLA	7		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Parallel group	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Crossover group	7	244	Std. Mean Difference (IV, Fixed, 95% CI)	-0.34 [-0.60, -0.08]
4 Symptom score (night time - SMD) - PLA	7		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Parallel group	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Crossover group	7	246	Std. Mean Difference (IV, Fixed, 95% CI)	-0.63 [-0.91, -0.35]
5 Symptom score (night time - SMD; estimated SDs) - PLA	7		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Parallel group	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Crossover group	7	246	Std. Mean Difference (IV, Fixed, 95% CI)	-0.58 [-0.85, -0.32]
6 Symptom score (cough - SMD) - PLA	3		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Parallel group	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Crossover group	3	102	Std. Mean Difference (IV, Fixed, 95% CI)	-0.51 [-0.99, -0.03]
7 Symptom score (activity - SMD) - PLA	2		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Parallel group	0		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Crossover group	2		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 FEV1 (SMD) - PLA	4		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Parallel group	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Crossover group	4	128	Std. Mean Difference (IV, Fixed, 95% CI)	0.33 [-0.03, 0.68]
9 PEF (SMD pm) - PLA	5		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 Parallel group	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Crossover group	5	204	Std. Mean Difference (IV, Fixed, 95% CI)	0.44 [0.14, 0.74]
10 PEF (am SMD) - PLA	5		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.1 Parallel group	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
10.2 Crossover group	5	204	Std. Mean Difference (IV, Fixed, 95% CI)	0.40 [0.10, 0.70]
11 PEF (clinic - SMD) - PLA	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.1 Parallel group	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Crossover group	2	82	Std. Mean Difference (IV, Fixed, 95% CI)	0.39 [-0.05, 0.83]
12 pm PEF (SMD estimated SDs) - PLA	5		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.1 Parallel group	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Crossover group	5	204	Std. Mean Difference (IV, Fixed, 95% CI)	0.41 [0.13, 0.69]
13 Symptom score (day wheeze) - ß	4		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
13.1 Crossover group	4	150	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.38, 0.27]
14 Symptom score (cough) - ß	3		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
14.1 Parallel group	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Crossover group	3	110	Std. Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.59, 0.16]
15 Symptom score (nighttime) - ß	4		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15.1 Parallel group	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 Crossover group (Rachelefsky night wheeze)	4	150	Std. Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.52, 0.12]
15.3 Crossover studies (Rachelefsky night shortness of breath)	4	150	Std. Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.53, 0.11]
15.4 Crossover studies (Rachelefsky night chest tightness)	4	150	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.51, 0.14]
15.5 Crossover studies (Rachelefsky night cough)	4	150	Std. Mean Difference (IV, Fixed, 95% CI)	-0.24 [-0.56, 0.08]
16 FEV1 - ß	3		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
16.1 Parallel group	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2 Crossover group	3	98	Std. Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.45, 0.34]
17 PEF (clinic) - ß	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
17.1 Parallel group	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.2 Crossover group	2	78	Std. Mean Difference (IV, Fixed, 95% CI)	0.19 [-0.26, 0.64]
18 Symptom score - SCG	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1 Parallel group	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.2 Crossover group	2	86	Std. Mean Difference (IV, Fixed, 95% CI)	0.39 [-0.04, 0.82]

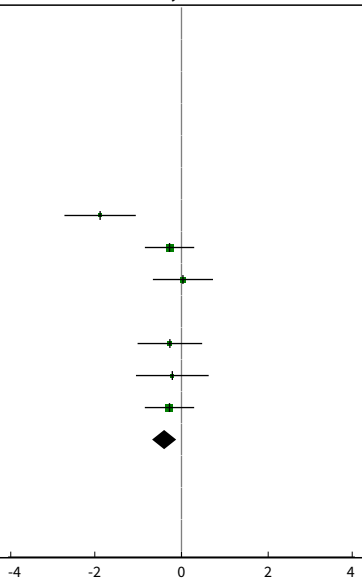
Analysis 8.1. Comparison 8 SMD comparisons, Outcome 1 Total symptom score (SMD) - PLA.

Study or subgroup	Xanthine N	Xanthine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
8.1.1 Parallel group							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.1.2 Crossover group							
Bose 1987	17	7.6 (0)	17	27.8 (0)			Not estimable
Conway 1986	16	57.8 (55.1)	16	55.3 (53.4)		36.04%	0.04[-0.65,0.74]
Edmunds 1980	30	2 (0.4)	30	2.3 (0.4)		63.96%	-0.65[-1.17,-0.13]
Subtotal ***	**63**		**63**			**100%**	**-0.4[-0.82,0.02]**
Heterogeneity: Tau^2=0; Chi^2=2.47, df=1(P=0.12); I^2=59.58%							
Test for overall effect: Z=1.88(P=0.06)							
Test for subgroup differences: Not applicable							



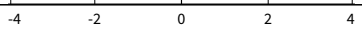
Analysis 8.2. Comparison 8 SMD comparisons, Outcome 2 Day symptom score (SMD) - PLA.

Study or subgroup	Xanthine N	Xanthine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
8.2.1 Parallel group							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.2.2 Crossover group							
Bose 1987	17	9.3 (7.3)	17	26.6 (10.5)		11.39%	-1.88[-2.7,-1.05]
Chow 1989	24	0.2 (0.3)	24	0.3 (0.4)		23.84%	-0.28[-0.84,0.29]
Conway 1986	16	42.8 (40.9)	16	41.4 (39.8)		16.06%	0.03[-0.66,0.73]
Glass 1981	16	2.3 (0)	16	2.2 (0)			Not estimable
Levene 1986	14	0.9 (0.9)	14	1.1 (0.9)		13.91%	-0.27[-1.01,0.48]
Nolan 1982	11	1.6 (0.7)	11	1.8 (0.9)		10.97%	-0.21[-1.05,0.63]
Wilson 1982	24	0.8 (1)	24	1.1 (1.1)		23.84%	-0.28[-0.85,0.29]
Subtotal ***	**122**		**122**			**100%**	**-0.4[-0.68,-0.12]**
Heterogeneity: Tau^2=0; Chi^2=14.56, df=5(P=0.01); I^2=65.67%							
Test for overall effect: Z=2.83(P=0)							
Test for subgroup differences: Not applicable							



Analysis 8.3. Comparison 8 SMD comparisons, Outcome 3 Symptom score (day symptoms, estimated SDs) - PLA.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
8.3.1 Parallel group							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.3.2 Crossover group							
Bose 1987	17	9.3 (7.3)	17	26.6 (10.5)		9.81%	-1.88[-2.7,-1.05]
Chow 1989	24	0.2 (0.3)	24	0.3 (0.4)		20.54%	-0.28[-0.84,0.29]
Conway 1986	16	42.8 (40.9)	16	41.4 (39.8)		13.83%	0.03[-0.66,0.73]
Glass 1981	16	2.3 (1.9)	16	2.2 (1.6)		13.84%	0.03[-0.66,0.72]
Levene 1986	14	0.9 (0.9)	14	1.1 (0.9)		11.98%	-0.27[-1.01,0.48]
Nolan 1982	11	1.6 (0.7)	11	1.8 (0.9)		9.45%	-0.21[-1.05,0.63]
Wilson 1982	24	0.8 (1)	24	1.1 (1.1)		20.54%	-0.28[-0.85,0.29]
Subtotal * **	**122**		**122**			**100%**	**-0.34[-0.6,-0.08]**
Heterogeneity: Tau^2=0; Chi^2=15.83, df=6(P=0.01); I^2=62.1%							
Test for overall effect: Z=2.59(P=0.01)							
Test for subgroup differences: Not applicable							

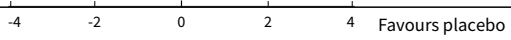


Analysis 8.4. Comparison 8 SMD comparisons, Outcome 4 Symptom score (night time - SMD) - PLA.

Study or subgroup	Xanthine N	Xanthine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
8.4.1 Parallel group							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.4.2 Crossover group							
Bose 1987	17	6.9 (3.6)	17	27 (12.1)		10.43%	-2.2[-3.08,-1.33]
Chow 1989	24	0.1 (0.2)	24	0.4 (0.5)		22.73%	-0.83[-1.42,-0.24]
Conway 1986	16	15 (15.1)	16	13.8 (14.9)		16.55%	0.08[-0.62,0.77]
Glass 1981	16	1.5 (0)	16	1.9 (0)			Not estimable
Levene 1986	15	0.8 (0.9)	15	1.3 (0.9)		14.9%	-0.54[-1.27,0.19]
Nolan 1982	11	2 (1.2)	11	2.6 (1.2)		11.02%	-0.47[-1.31,0.38]
Wilson 1982	24	0.3 (0.4)	24	0.5 (0.4)		24.37%	-0.38[-0.95,0.19]
Subtotal * **	**123**		**123**			**100%**	**-0.63[-0.91,-0.35]**
Heterogeneity: Tau^2=0; Chi^2=17.87, df=5(P=0); I^2=72.02%							
Test for overall effect: Z=4.37(P<0.0001)							
Test for subgroup differences: Not applicable							

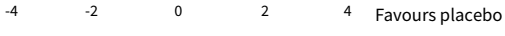
Analysis 8.5. Comparison 8 SMD comparisons, Outcome 5 Symptom score (night time - SMD; estimated SDs) - PLA.

Study or subgroup	Xanthine N	Xanthine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
8.5.1 Parallel group							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.5.2 Crossover group							
Bose 1987	17	6.9 (3.6)	17	27 (12.1)		8.97%	-2.2[-3.08,-1.33]
Chow 1989	24	0.1 (0.2)	24	0.4 (0.5)		19.54%	-0.83[-1.42,-0.24]
Conway 1986	16	15 (15.1)	16	13.8 (14.9)		14.22%	0.08[-0.62,0.77]
Glass 1981	16	1.5 (1.3)	16	1.9 (1.3)		14.04%	-0.31[-1.01,0.39]
Levene 1986	15	0.8 (0.9)	15	1.3 (0.9)		12.81%	-0.54[-1.27,0.19]
Nolan 1982	11	2 (1.2)	11	2.6 (1.2)		9.47%	-0.47[-1.31,0.38]
Wilson 1982	24	0.3 (0.4)	24	0.5 (0.4)		20.95%	-0.38[-0.95,0.19]
Subtotal ***	**123**		**123**			**100%**	**-0.58[-0.85,-0.32]**
Heterogeneity: Tau^2=0; Chi^2=18.56, df=6(P=0); I^2=67.67%							
Test for overall effect: Z=4.38(P<0.0001)							
Test for subgroup differences: Not applicable							



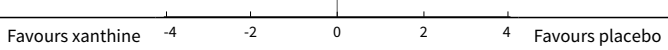
Analysis 8.6. Comparison 8 SMD comparisons, Outcome 6 Symptom score (cough - SMD) - PLA.

Study or subgroup	Xanthine N	Xanthine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
8.6.1 Parallel group							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.6.2 Crossover group							
Chow 1989	24	0.2 (0.3)	24	0.3 (0.4)		72.06%	-0.27[-0.84,0.3]
Glass 1981	16	3 (0)	16	4 (0)			Not estimable
Nolan 1982	11	3.5 (1.2)	11	4.9 (1.2)		27.94%	-1.13[-2.04,-0.22]
Subtotal ***	**51**		**51**			**100%**	**-0.51[-0.99,-0.03]**
Heterogeneity: Tau^2=0; Chi^2=2.44, df=1(P=0.12); I^2=58.99%							
Test for overall effect: Z=2.08(P=0.04)							
Test for subgroup differences: Not applicable							



Analysis 8.7. Comparison 8 SMD comparisons, Outcome 7 Symptom score (activity - SMD) - PLA.

Study or subgroup	Xanthine N	Xanthine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Std. Mean Difference Fixed, 95% CI
8.7.1 Parallel group						
8.7.2 Crossover group						



Study or subgroup	Xanthine N	Xanthine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Std. Mean Difference Fixed, 95% CI
Chow 1989	24	0.1 (0.2)	24	0.2 (0.3)		-0.22[-0.78,0.35]
Glass 1981	16	1.3 (0)	16	2.1 (0)		Not estimable

Favours xanthine -4 -2 0 2 4 Favours placebo

Analysis 8.8. Comparison 8 SMD comparisons, Outcome 8 FEV1 (SMD) - PLA.

Study or subgroup	Xanthine N	Xanthine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
8.8.1 Parallel group							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.8.2 Crossover group							
Chow 1989	24	1.6 (0.7)	24	1.5 (0.5)		38.34%	0.18[-0.38,0.75]
Gil 1993	9	2.5 (0.7)	9	2.5 (0.8)		14.41%	-0.12[-1.04,0.81]
Pedersen 1983	17	77.8 (18.1)	17	62.4 (21.6)		25.23%	0.76[0.06,1.46]
Strang 1960	14	65.6 (13.3)	14	60.5 (13.3)		22.02%	0.37[-0.38,1.12]
Subtotal ***	**64**		**64**			**100%**	**0.33[-0.03,0.68]**
Heterogeneity: Tau^2=0; Chi^2=2.61, df=3(P=0.46); I^2=0%							
Test for overall effect: Z=1.82(P=0.07)							
Test for subgroup differences: Not applicable							

Favours placebo -4 -2 0 2 4 Favours xanthine

Analysis 8.9. Comparison 8 SMD comparisons, Outcome 9 PEF (SMD pm) - PLA.

Study or subgroup	Xanthine N	Xanthine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
8.9.1 Parallel group							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.9.2 Crossover group							
Chow 1989	24	286 (59)	24	262 (62)		27.87%	0.39[-0.18,0.96]
Edmunds 1980	30	91 (5.5)	30	86 (5.5)		32.08%	0.9[0.37,1.43]
Levene 1986	14	90.5 (0)	14	85.2 (0)			Not estimable
MacDonald 1979	10	198 (81.6)	10	168.5 (69.2)		11.6%	0.37[-0.51,1.26]
Wilson 1982	24	91 (21.6)	24	91 (18.1)		28.45%	0[-0.57,0.57]
Subtotal ***	**102**		**102**			**100%**	**0.44[0.14,0.74]**
Heterogeneity: Tau^2=0; Chi^2=5.24, df=3(P=0.15); I^2=42.79%							
Test for overall effect: Z=2.86(P=0)							
Test for subgroup differences: Not applicable							

Favours placebo -4 -2 0 2 4 Favours xanthine

Analysis 8.10. Comparison 8 SMD comparisons, Outcome 10 PEF (am SMD) - PLA.

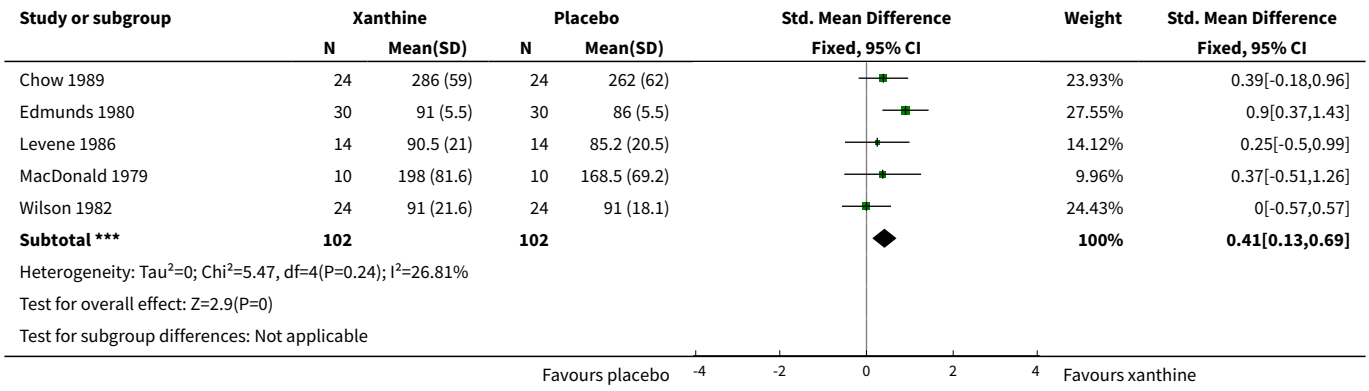
Study or subgroup	Xanthine N	Xanthine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
8.10.1 Parallel group							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.10.2 Crossover group							
Chow 1989	24	287 (60)	24	258 (64)		27.38%	0.46[-0.11,1.03]
Edmunds 1980	30	88 (5.5)	30	84 (5.5)		32.93%	0.72[0.2,1.24]
Levene 1986	14	90.1 (0)	14	83.4 (0)			Not estimable
MacDonald 1979	10	178.7 (66.4)	10	154 (70.7)		11.52%	0.35[-0.54,1.23]
Wilson 1982	24	86 (19.5)	24	86 (18.5)		28.17%	0[-0.57,0.57]
Subtotal ***	**102**		**102**			**100%**	**0.4[0.1,0.7]**
Heterogeneity: Tau^2=0; Chi^2=3.42, df=3(P=0.33); I^2=12.19%							
Test for overall effect: Z=2.63(P=0.01)							
Test for subgroup differences: Not applicable							

Analysis 8.11. Comparison 8 SMD comparisons, Outcome 11 PEF (clinic - SMD) - PLA.

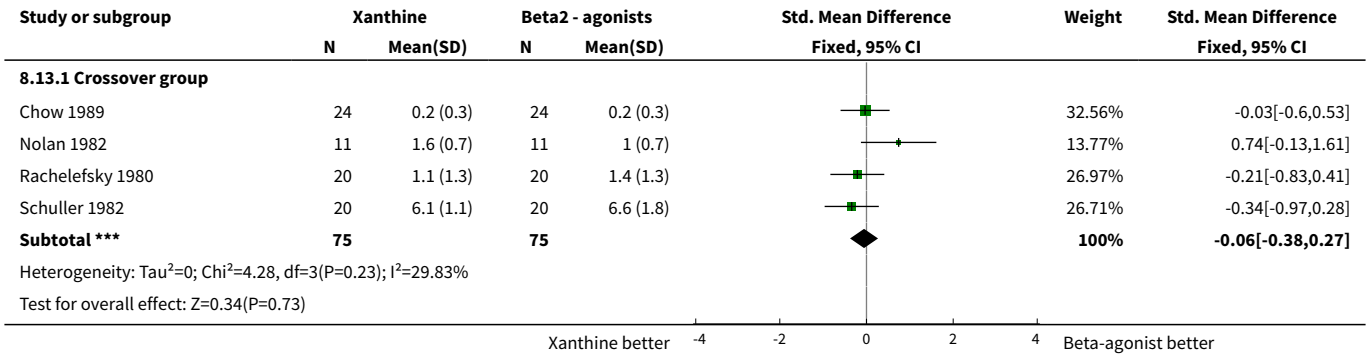
Study or subgroup	Xanthine N	Xanthine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
8.11.1 Parallel group							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.11.2 Crossover group							
Chow 1989	24	296 (73)	24	281 (68)		59.82%	0.21[-0.36,0.78]
Pedersen 1983	17	85.7 (16.6)	17	73.7 (19.2)		40.18%	0.66[-0.04,1.35]
Subtotal ***	**41**		**41**			**100%**	**0.39[-0.05,0.83]**
Heterogeneity: Tau^2=0; Chi^2=0.96, df=1(P=0.33); I^2=0%							
Test for overall effect: Z=1.74(P=0.08)							
Test for subgroup differences: Not applicable							

Analysis 8.12. Comparison 8 SMD comparisons, Outcome 12 pm PEF (SMD estimated SDs) - PLA.

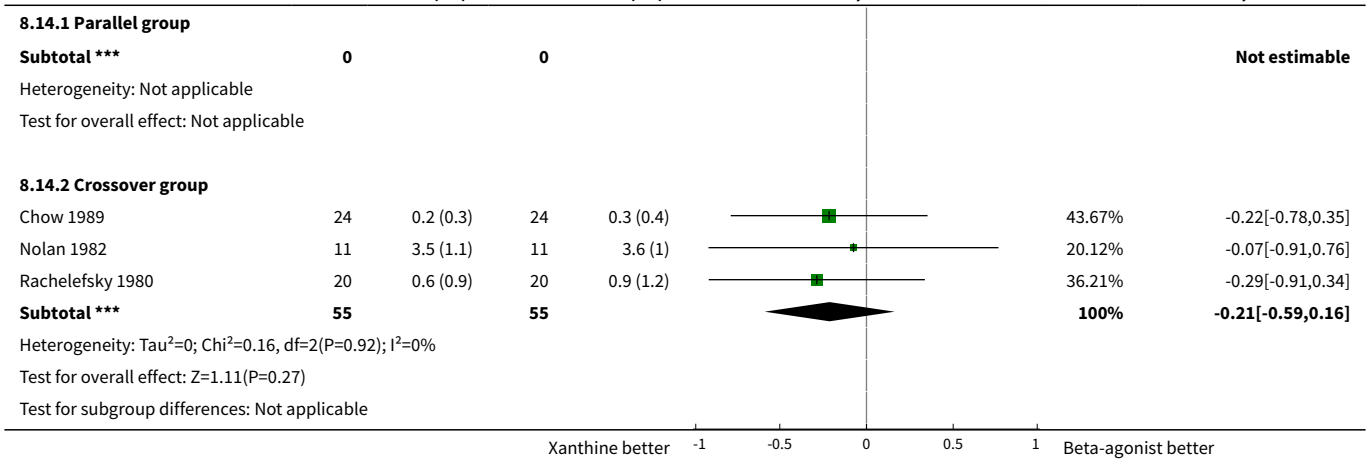
Study or subgroup	Xanthine N	Xanthine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
8.12.1 Parallel group							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.12.2 Crossover group							



Analysis 8.13. Comparison 8 SMD comparisons, Outcome 13 Symptom score (day wheeze) - ß.

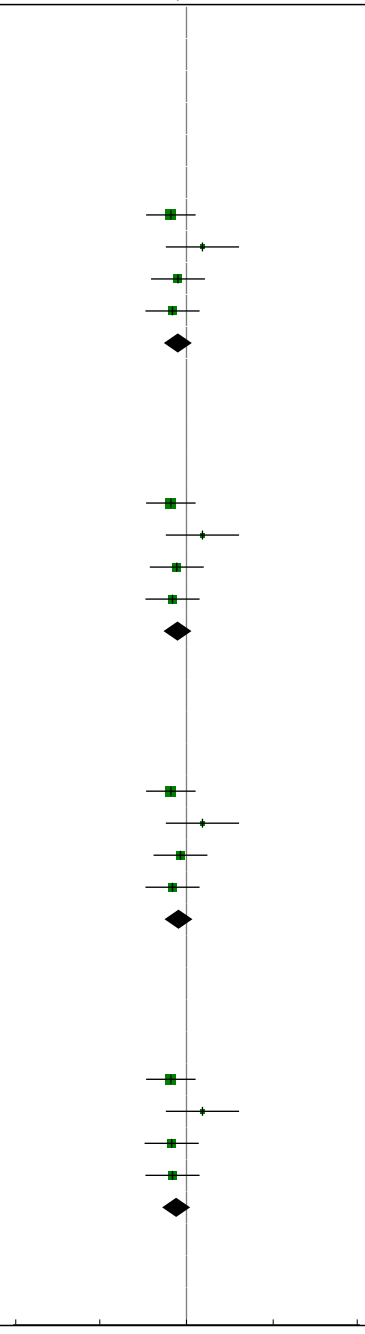


Analysis 8.14. Comparison 8 SMD comparisons, Outcome 14 Symptom score (cough) - ß.



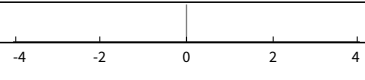
Analysis 8.15. Comparison 8 SMD comparisons, Outcome 15 Symptom score (nighttime) - ß.

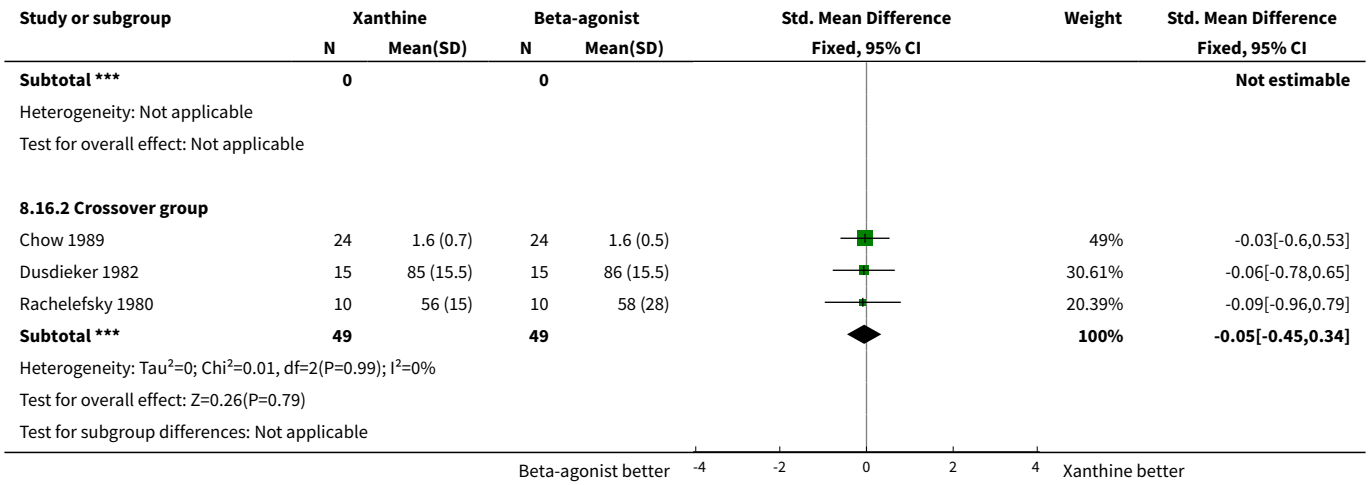
Study or subgroup	Xanthine N	Xanthine Mean(SD)	Beta-agonist N	Beta-agonist Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
8.15.1 Parallel group							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.15.2 Crossover group (Rachelefsky night wheeze)							
Chow 1989	24	0.1 (0.2)	24	0.2 (0.3)		31.88%	-0.36[-0.93,0.21]
Nolan 1982	11	1.9 (1)	11	1.5 (0.8)		14.57%	0.37[-0.48,1.21]
Rachelefsky 1980	20	1.1 (1.3)	20	1.4 (1.4)		26.9%	-0.2[-0.82,0.43]
Schuller 1982	20	6 (1.4)	20	6.6 (1.9)		26.65%	-0.32[-0.95,0.3]
Subtotal ***	**75**		**75**			**100%**	**-0.2[-0.52,0.12]**
Heterogeneity: Tau^2=0; Chi^2=2.19, df=3(P=0.53); I^2=0%							
Test for overall effect: Z=1.22(P=0.22)							
8.15.3 Crossover studies (Rachelefsky night shortness of breath)							
Chow 1989	24	0.1 (0.2)	24	0.2 (0.3)		31.9%	-0.36[-0.93,0.21]
Nolan 1982	11	1.9 (1)	11	1.5 (0.8)		14.58%	0.37[-0.48,1.21]
Rachelefsky 1980	20	0.5 (0.9)	20	0.8 (1.1)		26.86%	-0.22[-0.85,0.4]
Schuller 1982	20	6 (1.4)	20	6.6 (1.9)		26.67%	-0.32[-0.95,0.3]
Subtotal ***	**75**		**75**			**100%**	**-0.21[-0.53,0.11]**
Heterogeneity: Tau^2=0; Chi^2=2.2, df=3(P=0.53); I^2=0%							
Test for overall effect: Z=1.26(P=0.21)							
8.15.4 Crossover studies (Rachelefsky night chest tightness)							
Chow 1989	24	0.1 (0.2)	24	0.2 (0.3)		31.86%	-0.36[-0.93,0.21]
Nolan 1982	11	1.9 (1)	11	1.5 (0.8)		14.56%	0.37[-0.48,1.21]
Rachelefsky 1980	20	0.7 (1.1)	20	0.9 (1.3)		26.95%	-0.14[-0.76,0.48]
Schuller 1982	20	6 (1.4)	20	6.6 (1.9)		26.63%	-0.32[-0.95,0.3]
Subtotal ***	**75**		**75**			**100%**	**-0.18[-0.51,0.14]**
Heterogeneity: Tau^2=0; Chi^2=2.22, df=3(P=0.53); I^2=0%							
Test for overall effect: Z=1.12(P=0.26)							
8.15.5 Crossover studies (Rachelefsky night cough)							
Chow 1989	24	0.1 (0.2)	24	0.2 (0.3)		31.97%	-0.36[-0.93,0.21]
Nolan 1982	11	1.9 (1)	11	1.5 (0.8)		14.61%	0.37[-0.48,1.21]
Rachelefsky 1980	20	0.6 (0.9)	20	1 (1.2)		26.68%	-0.34[-0.97,0.28]
Schuller 1982	20	6 (1.4)	20	6.6 (1.9)		26.73%	-0.32[-0.95,0.3]
Subtotal ***	**75**		**75**			**100%**	**-0.24[-0.56,0.08]**
Heterogeneity: Tau^2=0; Chi^2=2.34, df=3(P=0.51); I^2=0%							
Test for overall effect: Z=1.45(P=0.15)							
Test for subgroup differences: Chi^2=0.06, df=1 (P=1), I^2=0%							



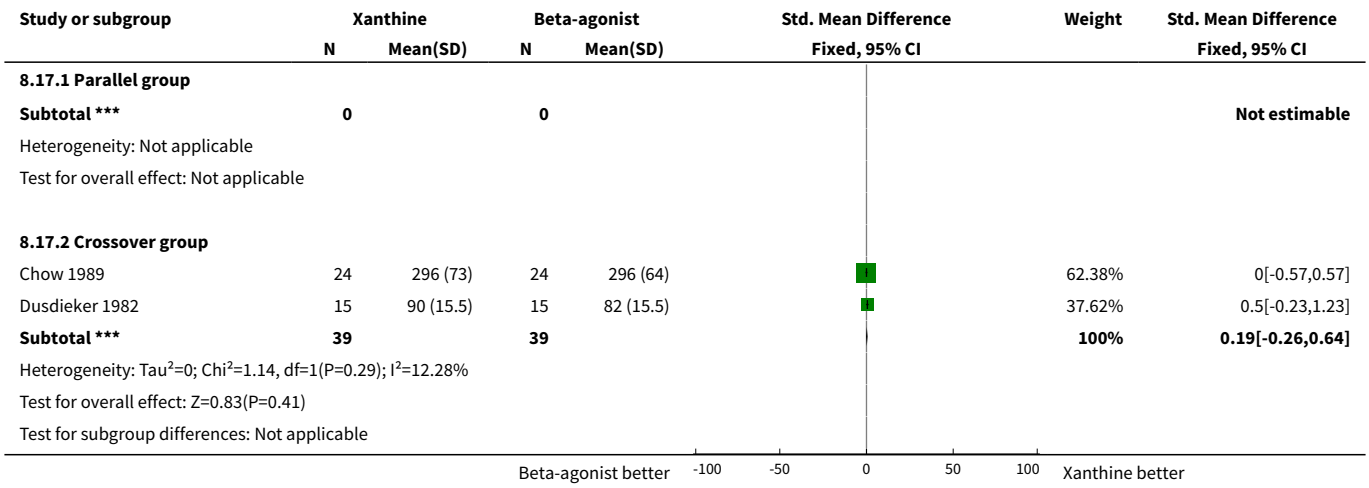
Analysis 8.16. Comparison 8 SMD comparisons, Outcome 16 FEV1 - ß.

Study or subgroup	Xanthine N	Xanthine Mean(SD)	Beta-agonist N	Beta-agonist Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
8.16.1 Parallel group							

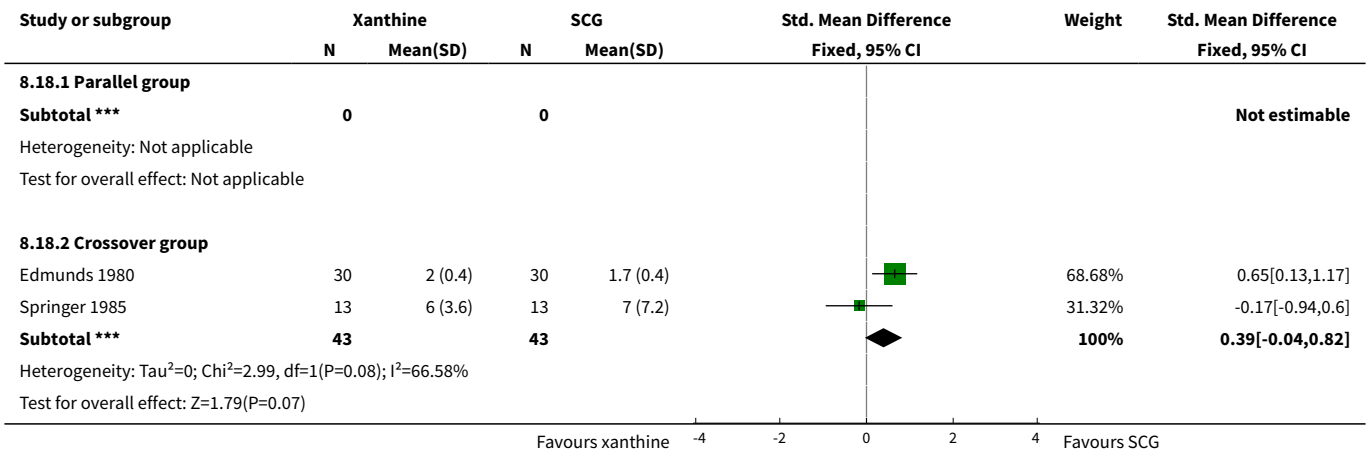


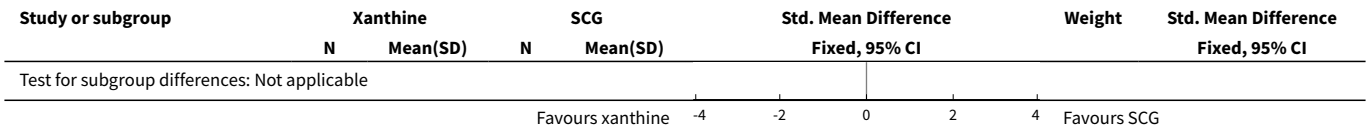


Analysis 8.17. Comparison 8 SMD comparisons, Outcome 17 PEF (clinic) - ß.



Analysis 8.18. Comparison 8 SMD comparisons, Outcome 18 Symptom score - SCG.





ADDITIONAL TABLES

Table 1. Imputations

Comparison & outcome	WMD/GIV	Study	Method
01:10 (Day symptoms, SD units)	GIV	Glass 1981	Average ratio of SD to mean from other studies
01:12 (Night symptoms, SD units)	GIV	Glass 1981	Average ratio of SD to mean from other studies
01:21 (Rescue medication usage, puffs/day)	GIV	Glass 1981	Published means; average pooled SD

WHAT'S NEW

Date	Event	Description
15 May 2008	New search has been performed	One new study was added to the review from searches conducted between May 2006 and May 2008; risk of bias tables has been added to the review. The conclusions of the review remain unchanged
7 April 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 2001
Review first published: Issue 1, 2006

Date	Event	Description
2 November 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

PS: Protocol initiation and development, study assessment, data extraction, interpretation
AB: Protocol development, study assessment, data extraction, data entry
TL: Data analysis, write-up
FD: Editorial support and critique for protocol and review

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Nederlands Astma Fonds, Netherlands.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The release of Review Manager 5 software in spring 2008 has also coincided with a number of changes to recommended methodological approaches in Cochrane reviews (see Handbook 2008). For this version of the review, we have provided an overview of the risk of bias for each study. Our judgements and the evidence we have based them on, are presented in tables accompanying the study characteristics. The source of the information that we have used as the basis for these judgements are either trial publications or correspondence with the study authors.

INDEX TERMS

Medical Subject Headings (MeSH)

Aminophylline [therapeutic use]; Anti-Asthmatic Agents [*therapeutic use]; Asthma [*drug therapy]; Bronchodilator Agents [therapeutic use]; Randomized Controlled Trials as Topic; Theophylline [therapeutic use]; Xanthines [*therapeutic use]

MeSH check words

Child; Humans